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* * * * * * * * * *   Welcome to STN International   * * * * * * * * * *

 NEWS  1           Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2           "Ask CAS" for self-help around the clock
 NEWS  3  FEB 28   PATDPAFULL - New display fields provide for legal status
                   data from INPADOC
 NEWS  4  FEB 28   BABS - Current-awareness alerts (SDIs) available
 NEWS  5  MAR 02   GBFULL: New full-text patent database on STN
 NEWS  6  MAR 03   REGISTRY/ZREGISTRY - Sequence annotations enhanced
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FILE 'HOME' ENTERED AT 11:40:40 ON 22 AUG 2005

=> file medline
COST IN U.S. DOLLARS                            SINCE FILE      TOTAL
                                                   ENTRY    SESSION
FULL ESTIMATED COST                                 0.42       0.42

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http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html

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```
=> s (HIV or human immunodeficiency virus)
        150421 HIV
       1278165 HUMAN
        119376 IMMUNODEFICIENCY
        398559 VIRUS
         46554 HUMAN IMMUNODEFICIENCY VIRUS
                 (HUMAN(W)IMMUNODEFICIENCY(W)VIRUS)
L1      155517 (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)

=> s l1 and (mucosal or IgA)
         57663 MUCOSAL
         32141 IGA
L2        1953 L1 AND (MUCOSAL OR IGA)

=> s l2 and (env? or gp160 or gp120 or gp41)
        395641 ENV?
          1493 GP160
          6286 GP120
          2395 GP41
L3         420 L2 AND (ENV? OR GP160 OR GP120 OR GP41)

=> s l3 and py<1997
      11060678 PY<1997
L4           99 L3 AND PY<1997

=> d l4,cbib,ab,1-99
```

L4 ANSWER 1 OF 99 MEDLINE on STN
2002602512. PubMed ID: 12290880. Breast milk transmission of **HIV**-1.
Nduati R; John G. NARESA monograph, **(1995 Dec)** (18) 1-3. Journal code: 9501763.
Report No.: PIP-111897; POP-00251589. Pub. country: Kenya. Language: English.

AB Breast milk provides infants and children immunologic, nutritional, and child spacing benefits. Yet it also transmits some viruses, for example, **HIV**-1. The World Health Organization recommends that, in conditions with poor access to breast milk substitutes, **HIV**-positive women should still breast feed due to the nutritional and infectious risk of artificial feeding. It appears that breast fed infants experience a slower progression of AIDS and death. Vertical transmission of **HIV**-1 may occur during pregnancy, at delivery, or through breast milk. The **HIV**-1 transmission rate via breast milk from acutely infected women is estimated to be 29-36%. A meta-analysis of case reports and small case series of women with chronic **HIV**-1 infection indicated a breast feeding transmission rate of 14%. Studies suggest that the likelihood of **HIV**-1 transmission via breast milk increases as duration of breast feeding increases. Infants with detectable **HIV**-1 DNA tend to have mothers whose absolute CD4 counts are less than 400 and have severe vitamin A deficiency. Breast milk has **HIV**-1 specific immunoglobulins (IgG, **IgA**, and IgM). It appears that **HIV**-1 elicits a local immune response. Breast milk of **HIV**-1 positive mothers with non-infected children tends to still have IgM and **IgA** until 18 months. Potential risk factors for breast milk transmission of **HIV**-1 include cracked nipples and mastitis in the mother; oral thrush, malnutrition, inflammation of the lips, and **mucosal** compromise in the infant; and vigorous suction of the neonate and use of the wrong equipment for suctioning. Inhibiting factors of **HIV**-1 in breast milk are bovine and human lactoferrin and a membrane associated protein that attaches to the CD4 receptor and thus prevents attachment of the **HIV** antigen **gp120** to the CD4 receptor on T-cells.

L4 ANSWER 2 OF 99 MEDLINE on STN
2001278322. PubMed ID: 11361717. **HIV** antibody responses in children of **HIV**-infected mothers. Sever J L; Rakusan T A; Campos J M; O'Donnell R M; Price V A. (Children's National Medical Center, Washington, DC, USA.) Pediatric AIDS and HIV infection, **(1996 Aug)** 7 (4) 246-53. Journal code: 9107942. ISSN: 1045-5418. Pub. country: United States. Language:

English.

AB About 25% of the children of untreated **HIV**-infected mothers are later determined to be **HIV**-infected. At birth, all of the children of **HIV**-infected mothers have **HIV**-IgG antibody, which is transferred transplacentally from the mothers to their children, and infected children produce **HIV**-IgG antibody in response to their infection. Most infected children have detectable **HIV-IgA** by 3 months of age. We have studied **HIV** antibody responses in three groups of children of **HIV**-infected mothers at 9 to 12 months and 15 to 24 months of age. The groups were classified by Centers for Disease Control and Prevention (CDC) criteria and included: (I) **HIV** seroreverters (SR); (II) **HIV**-infected; Non- to mildly symptomatic (N+A); and (III) **HIV**-infected; Moderately to Severely Symptomatic (B+C). **HIV**-IgG antibody was detected in some SR children at low titer levels (10 to 20) through 11 months of age but not at 12 or later. For both the N+A and B+C groups, there were no significant changes in the mean **HIV**-IgG titers from 9-12 to 15-24 months of age. Also, no significant difference in titers were found between the two infected groups for both age groups. **HIV-IgA** antibody responses were more frequently positive at 15 to 24 months for all seven antigens studied for the N+A than the B+C patients; however, statistical significance was attained only for **gp41** ($p < or = 0.01$). N+A children showed more responses to the viral antigens at 15-24 months than at 9-12 months. This increase in **HIV**-specific **IgA** among the N+A children may be important in restricting their **HIV** infections. Total IgG levels were significantly higher in the **HIV**-infected groups than in the SR ($p < or = 0.0001$), but no differences were detected between the N+A and B+C groups. Total **IgA** increased over time in the N+A patients from 9-12 to 15-24 months. A similar trend was apparent in the B+C group, but did not reach statistical significance. Both N+A and B+C patients at 15-24 months had significantly higher total **IgA** levels than did the SR at 9-12 months of age. The B+C group had significantly lower CD4 counts for both age groups than did the N+A or SR groups ($p < or = 0.0001$).

L4 ANSWER 3 OF 99 MEDLINE on STN

1998040680. PubMed ID: 9373349. Induction of **mucosal** anti-**HIV** antibodies by facilitated transfection of airway epithelium with lipospermine/DNA complexes. Mitchell W M; Rosenbloom S T; Gabriel J. (Department of Pathology, Vanderbilt University, Nashville, TN 37232, USA.) Immunotechnology : an international journal of immunological engineering, **(1995 Dec)** 1 (3-4) 211-9. Journal code: 9511979. ISSN: 1380-2933. Pub. country: Netherlands. Language: English.

AB BACKGROUND: Expression of microbial protein sequences in eukaryotic cells transfected by transcriptional/translational permissive cDNA constructs can induce systemic humoral and cellular responses in vivo. Two methods of in vivo transfection have been described to date. One method uses large quantities of naked DNA injected into skeletal muscle. The second method uses relatively small quantities of DNA complexed to gold particles for bollistic penetration of the plasma membrane of keratinocytes. The major disadvantage of the bolistic method is that instrumentation is required which is not generally available. OBJECTIVES: The objectives of this study were to determine whether the use of DNA complexed with a cationic lipopolyamine could reduce the quantity of DNA required to induce systemic humoral responses following muscle transfection and whether similar DNA/lipopolyamine complexes could induce **mucosal** humoral responses following airway exposure. STUDY DESIGN: Balb/c mice were exposed by nasal aerosol or intramuscular inoculation to a mammalian transcriptional/translational permissive DNA construct containing the entire sequence for the **HIV-1 envelope** polyprotein. Experimental animals were further segregated by the number of exposures at 3-week intervals and whether the DNA was complexed to dioctadecylamidoglycylspermine (DOGS) at a 5:1 molar charge ratio of DOGS/DNA. RESULTS: DOGS facilitated in vivo transfection of mouse muscle reduced the quantity of DNA required for a systemic humoral response to surface expressed **HIV-envelope** proteins by one order of magnitude. Exposure of airway mucosa to both 10 micrograms and 1 microgram quantities of DNA complexed to DOGS produced systemic humoral responses to **HIV-envelope** as well as **mucosal** antibodies in pulmonary and colonic epithelia. Molecular modeling of DOGS/DNA complexes at the 5:1 charge ratio used in this study indicates that the DNA component is not exposed to aqueous solvents and may be relatively resistant to degradation under common biological **environments**. CONCLUSION: Facilitated transfer of DNA by DOGS to transcriptional/translational competent cells offers several distinct advantages to the use of DNA alone. Since significantly smaller amounts of DNA are required, the potential for the induction of antibodies against DNA itself lessens the likelihood for the development of a lupus-like syndrome. More importantly, however, is the apparent ability to transfect **mucosal** cells which results in the development of specific **mucosal** immune responses. This procedure may allow the development of general methods for the induction of **mucosal** immunity at the level of

entry for **mucosal** pathogens without the disadvantages inherent in live attenuated vectors.

L4 ANSWER 4 OF 99 MEDLINE on STN

1998040661. PubMed ID: 9373330. Human monoclonal Fab fragments specific for viral antigens from combinatorial **IgA** libraries. Moreno de Alboran I; Martinez-alonso C; Barbas C F 3rd; Burton D R; Ditzel H J. (Department of Immunology, Scripps Research Institute, La Jolla, CA 92037, USA.) Immunotechnology : an international journal of immunological engineering, **(1995 May)** 1 (1) 21-8. Journal code: 9511979. ISSN: 1380-2933. Pub. country: Netherlands. Language: English.

AB BACKGROUND: **IgA** constitutes the first line of immune defense, interacting with a variety of **environmental** antigens. Following infection with respiratory syncytial virus (RSV) individuals frequently exhibit elevated serum **IgA** titers specific for the virus. Previously combinatorial IgG libraries have successfully been used to clone such human antibody responses. OBJECTIVES: Here we evaluate the possibility of constructing combinatorial **IgA** libraries on the surface of filamentous phage to retrieve human viral-specific **IgA** Fab fragments. STUDY DESIGN: Bone marrow from an **HIV**-1 seropositive donor was used as RNA source to construct combinatorial **IgA** kappa and lambda libraries of approximately 10(7) clones. RESULTS: By affinity selection using an immobilized recombinant RSV FG protein, two unique **IgA** Fab fragments producing clones (AD5 and AD23) reactive with the selecting antigen were isolated. One of the Fab fragments was found to be specific for RSV F glycoprotein and bind with high apparent affinity (2 x 10(8) M-1). The other binds with lower affinity and exhibits cross-reactivity with other antigens. CONCLUSION: The strategy described, involving construction of combinatorial **IgA** libraries on the surface of filamentous phage, should be generally applicable to the investigation of both **mucosal** and systemic human **IgA** immune responses, and may become an important tool for evaluation of **mucosal** vaccine regimes.

L4 ANSWER 5 OF 99 MEDLINE on STN

1998038634. PubMed ID: 9371296. Non-Hodgkin's lymphoma. Longo D L. (Biological Response Modifiers Program, National Cancer Institute, Frederick Cancer Research and Development Center, MD 21702-1201, USA.) Current opinion in hematology, **(1994 Jul)** 1 (4) 295-302. Ref: 54. Journal code: 9430802. ISSN: 1065-6251. Pub. country: United States. Language: English.

AB The increasing incidence of lymphomas is related to **environmental** factors including occupational exposures and **HIV** infection. Molecular and immunologic studies have recently defined some new clinico-pathologic entities such as mantle cell lymphoma and lymphoma of **mucosal**-associated lymphatic tissue. However, the most prevalent lymphomas are follicular lymphomas and diffuse aggressive-histology lymphomas. Follicular lymphomas are curable with radiation therapy when they are localized to lymph nodes. Efforts to improve treatment results in patients with advanced follicular lymphoma are focusing primarily on the use of additional therapy (eg, interferon, high-dose chemoradiotherapy, and immunologic therapy) after induction of a complete response by combination chemotherapy. Aggressive-histology lymphoma is curable in more than 85% of patients when it is localized and in more than 50% of patients when it is disseminated. Efforts to improve treatment results are focusing primarily on delivering therapy with higher-dose intensity.

L4 ANSWER 6 OF 99 MEDLINE on STN

97079143. PubMed ID: 8920875. Long-lived cytotoxic T lymphocyte memory in **mucosal** tissues after **mucosal** but not systemic immunization. Gallichan W S; Rosenthal K L. (Department of Pathology, McMaster University Health Sciences Centre, Hamilton, Ontario, Canada.) Journal of experimental medicine, **(1996 Nov 1)** 184 (5) 1879-90. Journal code: 2985109R. ISSN: 0022-1007. Pub. country: United States. Language: English.

AB The induction and maintenance of long-term CTL memory at **mucosal** surfaces may be a critical component of protection against **mucosal** pathogens and is one goal towards development of effective **mucosal** vaccines. In these studies we have functionally evaluated short and long-term CTL memory in systemic and respiratory or genital-associated lymphoid tissues following **mucosal** or systemic routes of immunization. Our results indicate that shortly after immunizing mice with a recombinant adenovirus vector expressing glycoprotein B (gB) of herpes simplex virus (AdgB8), gB-specific CTL memory responses were observed in systemic and **mucosal** immune compartments regardless of the route of inoculation. In contrast, several months after immunization, anamnestic CTL responses compartmentalized exclusively to **mucosal** or systemic lymphoid tissues after **mucosal** or systemic immunization, respectively. Furthermore, the compartmentalized CTL memory responses in **mucosal** tissues were functionally observed for longer than 1.5 yr after intranasal immunization, and CTL precursor frequencies one year after immunization

were comparable to those seen shortly after immunization. Therefore, to our knowledge, this is the first functional demonstration that the maintenance of anti-viral memory CTL in **mucosal** tissues is dependent on the route of immunization and the time of assessment. These results have important implications for our understanding of the development, maintenance, and compartmentalization of functional T cell memory and the development and evaluation of vaccines for **mucosal** pathogens, such as HSV and **HIV**.

L4 ANSWER 7 OF 99 MEDLINE on STN
97071928. PubMed ID: 8914773. Salivary binding antibodies induced by **human immunodeficiency virus** type 1 recombinant **gp120** vaccine. The NIAID AIDS Vaccine Evaluation Group. Gorse G J; Yang E Y; Belshe R B; Berman P W. (Department of Internal Medicine, Saint Louis University School of Medicine, Missouri, USA.) Clinical and diagnostic laboratory immunology, **(1996 Nov)** 3 (6) 769-73. Journal code: 9421292. ISSN: 1071-412X. Pub. country: United States. Language: English.
AB Salivary binding antibodies induced by candidate **human immunodeficiency virus** type 1 (**HIV**-1) vaccines in healthy, **HIV**-1 uninfected volunteers were assessed in a clinical trial evaluating intramuscularly injected **HIV**-1MN recombinant **gp120** (rgp120) vaccine alone or with **HIV**-1IIIB rgp120 vaccine. The two rgp120 vaccines induced **envelope** glycoprotein-specific immunoglobulin G (IgG) and **IgA** antibodies in whole saliva and serum.

L4 ANSWER 8 OF 99 MEDLINE on STN
97045423. PubMed ID: 8890473. Cervicovaginal anti-**HIV** antibodies in index women from **HIV**-discordant, exclusively heterosexual, couples. Belec L; Prazuck T; Payan C; Mohamed A S; Cancre N; Hocini H; Malkin J E; Pillot J. (Laboratoire de Virologie, Centre Hospitalo-Universitaire (CHU) Broussais, Paris, France.) Viral immunology, **(1996)** 9 (3) 155-8. Journal code: 8801552. ISSN: 0882-8245. Pub. country: United States. Language: English.
AB Cervicovaginal **IgA** and IgG anti-**gp160** antibodies were evaluated in cervicovaginal secretions from twelve **HIV**-discordant heterosexual couples, matched with twelve **HIV**-concordant heterosexual couples, at similar stage of **HIV** disease. The mean reciprocal end-point titers of cervicovaginal **IgA** or IgG to **gp160** were similar in cases and in controls. These observations suggest that cervicovaginal antibodies to **HIV** do not appear as biological indicators sufficiently relevant to explain a possible reduced infectivity of the female index case in **HIV**-discordant couples, by comparison with **HIV**-concordant couples.

L4 ANSWER 9 OF 99 MEDLINE on STN
97023864. PubMed ID: 8870185. Vaginal and rectal infection of cats with feline immunodeficiency virus. Bishop S A; Stokes C R; Gruffydd-Jones T J; Whiting C V; Harbour D A. (Department of Clinical Veterinary Science, University of Bristol, Langford, Avon, UK.) Veterinary microbiology, **(1996 Aug)** 51 (3-4) 217-27. Journal code: 7705469. ISSN: 0378-1135. Pub. country: Netherlands. Language: English.
AB The objective of this study was to examine the potential of vaginal and rectal **mucosal** routes for feline immunodeficiency virus (FIV) uptake and infection, as a model of **mucosal HIV** infection, and to determine the fate of virus at these **mucosal** sites following transmission of infection. SPF cats were exposed to FIV isolates (PET, GL-8, T637), administered as either cell-associated or cell-free inocula, via the rectum or vagina. Establishment of infection was confirmed by isolation of infectious FIV from peripheral blood mononuclear cells (PBMC), and by presence of FIV proviral DNA in PBMC using a nested polymerase chain reaction. Fate of virus in tissue taken at necropsy from cats infected for 6-48 weeks was assessed by localizing FIV core and **envelope** proteins, p24 and **gp41**, using a biotin-streptavidin linked immunoperoxidase (IP) technique. Cells susceptible to infection were identified by an in situ hybridization technique for FIV viral DNA and RNA. Cell-free, as well as cell-associated, virus was infectious across intact vaginal and rectal **mucosal** surfaces. Transmission was most successful using cell-associated inocula, and via the rectal route. Cells infected with FIV were detected by IP staining in the colon of 6/9 rectally challenged cats and 1/5 vaginally challenged cats. Virus was predominantly localized within the epithelium at the base of the colonic crypts associated with lymphoid aggregates (follicle associated epithelium; FAE), and within the lymphoid follicle itself. Occasional infected cells were also noted within the lamina propria. The distribution of FIV DNA positive cells in the colon was similar to that for FIV antigen whilst FIV RNA positive cells were found more extensively, including within the lamina propria and lymphoid follicle. FIV infected cells were not detected within the vagina, or colonic and ileac lymph nodes. Similar patterns of infected cells were seen in all of the positive cats, indicating that colonic tissues remain persistently

actively infected with FIV. We conclude that the FIV/cat model of rectal and vaginal **mucosal** infection should prove useful for characterizing the mechanism by which **HIV** infects **mucosal** surfaces and as a challenge system for the design of vaccines effective at preventing **HIV** infection via rectal and vaginal routes.

L4 ANSWER 10 OF 99 MEDLINE on STN
97000547. PubMed ID: 8843632. Influence of phospholipid composition on antibody responses to liposome encapsulated protein and peptide antigens. Phillips N C; Gagne L; Ivanoff N; Riveau G. (Faculte de pharmacie, Universite de Montreal, Quebec, Canada.) Vaccine, **(1996 Jun)** 14 (9) 898-904. Journal code: 8406899. ISSN: 0264-410X. Pub. country: ENGLAND: United Kingdom. Language: English.
AB The effect of phospholipid composition on mouse IgG antibody responses to liposomal bovine serum albumin (BSA), murine monoclonal antibody GK1.5 (anti-CD4) or a 21 amino acid peptide from the second conserved domain of **HIV gp120** after s.c. administration, and on the **IgA**, IgE, and IgG antibody response to liposomal Shistosoma mansoni glutathione-S-transferase (Sm28GST) after oral administration, was determined. Antibody responses were compared with alum-adsorbed and N-acetylmuramyl-L-alanyl-D-isoglutamine (MDP)-antigen mixtures. For the s.c. route, dipalmitoylphosphatidylcholine (DPPC)/dimyristoylphosphatidylglycerol (DMPG) liposomes induced 54-60% IgG1 and 35-44% IgG(2a+2b). DPPC/dipalmitoylphosphatidylethanolamine (DPPE) liposomes induced 73-78% IgG1 and 15-25% IgG(2a+2b). DPPC/ phosphatidylserine (PS) liposomes induced 86-89% IgG1 and 8-12% IgG(2a+2b). Alum and MDP induced 79-91% IgG1 and 4-17% IgG(2a+2b). The rank order of adjuvanticity for induction of IgG antibody was DPPC/DMPGDPPC/PE > > alum > > MDPDPPC/PS for all three antigens. DPPC/DMPG liposomes were the only effective adjuvant for the induction of secretory **IgA** and circulatory IgE and IgG antibodies against Sm28GST after oral administration. The failure of liposome-antigen mixtures to elicit an antibody response showed that liposomal incorporation of the antigens was obligatory for adjuvant activity. These results demonstrate that the correlation between phospholipid composition and adjuvanticity is independent of liposome charge, antigen, or route of administration.

L4 ANSWER 11 OF 99 MEDLINE on STN
96431378. PubMed ID: 8834460. Distinct but related **human immunodeficiency virus** type 1 variant populations in genital secretions and blood. Overbaugh J; Anderson R J; Ndinya-Achola J O; Kreiss J K. (Department of Microbiology, University of Washington, Seattle 98195, USA.) AIDS research and human retroviruses, **(1996 Jan 20)** 12 (2) 107-15. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.
AB For a **HIV** vaccine to be effective, it will be essential that it protect against the virus variants to which individuals are most frequently exposed. **HIV**-1 is predominantly a sexually acquired virus, thus, variants in genital secretions are a potentially important reservoir of viruses that are transmitted. Because there are no data available on variants in the genital mucosa, we analyzed this provirus population and compared it to the proviruses in the blood of individuals chronically infected with **HIV**-1. A major genetic difference between variants within a patient were insertions, which were apparently created by duplication of adjacent sequences, that resulted in acquisition of new potential glycosylation sites in V1 and V2. Comparisons of **mucosal** and PBMC variants suggest that these tissues harbor distinct, but related populations of **HIV**-1 variants. In two of three patients, the **mucosal** variants were most closely related to a minor variant genotype in blood. In a third individual, viruses in both tissues were surprisingly homogeneous, but the majority of variants in the cervix encoded a V1 sequence with a predicted glycosylation pattern similar to a minor variant in blood. The V3 sequence patterns of the **mucosal** isolates indicate they may be predominantly macrophage-tropic viruses.

L4 ANSWER 12 OF 99 MEDLINE on STN
96424754. PubMed ID: 8827215. Protection against **mucosal** SIVsm challenge in macaques infected with a chimeric SIV that expresses **HIV** type 1 **envelope**. Quesada-Rolander M; Makitalo B; Thorstensson R; Zhang Y J; Castanos-Velez E; Biberfeld G; Putkonen P. (Swedish Institute for Infectious Disease Control, Karolinska Institute, Stockholm, Sweden.) AIDS research and human retroviruses, **(1996 Jul 20)** 12 (11) 993-9. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.
AB In a monkey model we used a chimeric SIV expressing the **HIV**-1 **envelope** gene (SHIV-4) as a live attenuated vaccine and a virulent SIVsm as a **mucosal** challenge. Four cynomolgus monkeys were inoculated intravenously with SHIV-4. Virus was repeatedly isolated from blood mononuclear cells of all four animals for 2 to 7 months after the

inoculation of SHIV. All monkeys developed neutralizing antibodies to **HIV**-1 and high antibody titers to **HIV**-1 **envelope** glycoproteins. In contrast, no neutralizing antibodies to SIVsm were detected and cross-reacting antibodies to SIV **envelope** glycoproteins were demonstrable in low titers. Nine to 12 months after the SHIV inoculation the four monkeys and six naive control monkeys were challenged intrarectally with 10 monkey infectious doses of macaque cell-grown SIVsm. After a follow-up period of 1 year, two of four SHIV-infected monkeys were completely protected against SIVsm infection as shown by repeated negative virus isolations and negative polymerase chain reaction for SIV **envelope** DNA. One naive monkey that received blood from the two protected monkeys showed no signs of infection. The remaining two SHIV-infected monkeys showed an initial infection on challenge with SIVsm, but viral replication was thereafter suppressed. Cytotoxic T lymphocytes to SIV Nef and RT were demonstrable in one of four SHIV-infected monkeys before SIVsm challenge, but this monkey was not protected against SIV infection. All six control animals yielded virus repeatedly after SIVsm challenge and three of them showed declining CD4 cell counts. Thus, infection with SHIV expressing **HIV**-1 **envelope** could induce cross-protection against **mucosal** SIVsm challenge.

L4 ANSWER 13 OF 99 MEDLINE on STN

96415933. PubMed ID: 8818840. Strategies for AIDS vaccines. Stott E J; Schild G C. (National Institute for Biological Standards and Control Potters Bar, Hertfordshire, UK.) Journal of antimicrobial chemotherapy, **(1996 May)** 37 Suppl B 185-98. Ref: 67. Journal code: 7513617. ISSN: 0305-7453. Pub. country: ENGLAND: United Kingdom. Language: English.

AB In the global AIDS epidemic, over half of all infections have occurred in people less than 25 years old resulting in profound social, economic and demographic consequences. Current estimates indicate that the present 15 million **HIV** infections will increase to over 30 million by the end of the millennium. For most countries a safe and effective vaccine offers the only hope of controlling the spread of this disease. The development of an effective vaccine against **HIV** is beset with formidable obstacles. Despite these difficulties, substantial progress has been made towards developing effective strategies for vaccination. Human clinical trials and animal models for AIDS, particularly simian immunodeficiency virus (SIV) infection of macaques, have proved invaluable in this quest. Inactivated virus vaccines induced potent protection in this model, but subsequent studies revealed that protection was mediated by antibody to cellular proteins present in the vaccine preparations and on the surface of infecting virions. This surprising observation has provided an alternative and complementary approach to the development of vaccines against **HIV** in man which is still being pursued. Live attenuated vaccines were initially dismissed as far too hazardous. However, the concept has recently been reexamined in the light of powerful evidence that attenuated SIV induces potent protection against a wide variety of viruses administered by intravenous or **mucosal** routes and even against challenge with viable virus-infected spleen cells. Efforts are now underway to understand the mechanism of this protection and to attempt to reproduce it by less hazardous means. Considerable effort has been devoted to the development of subunit **HIV** vaccines, predominantly based on the **envelope** glycoproteins of the virus. Extensive clinical trials in human volunteers have established that these vaccines are safe and antigenic. However, the immune responses appear to be transient and the antibodies induced do not neutralize the primary isolates of **HIV** which are circulating in the population. There are now three possible approaches to an AIDS vaccine which are being actively pursued.

L4 ANSWER 14 OF 99 MEDLINE on STN

96407302. PubMed ID: 8811355. Correlates of protective immunity against **HIV**-1 infection in immunized chimpanzees. Murthy K K; Cobb E K; Rouse S R; Lunceford S M; Johnson D E; Galvan A R. (Department of Virology and Immunology, Southwest Foundation for Biomedical Research, San Antonio, TX 78228-0147, USA.) Immunology letters, **(1996 Jun)** 51 (1-2) 121-4. Ref: 27. Journal code: 7910006. ISSN: 0165-2478. Pub. country: Netherlands. Language: English.

AB Several experimental vaccination strategies have been developed to prevent primary infection with **human immunodeficiency virus** (**HIV**), and as immunotherapeutics for infected individuals. Many of the putative vaccines have been tested in chimpanzees (p. troglodytes) to determine their safety, efficacy, and to delineate immune correlates of protection. To date, approximately 25 candidate vaccines representing active or passive strategies have been evaluated in chimpanzees, and efficacy has been based on protection against primary infection following intravenous or **mucosal** challenge with cell-free or cell-associated virus. Active immunization has been attempted with whole inactivated virus, **envelope** depleted viral preparation, vaccinia vector expressing gp 160 in combination with other viral gene products, and subunit vaccines

containing recombinant gp 120 derived from different isolates. Polyclonal and monoclonal antibodies with neutralizing activity have been utilized for pre- and post-exposure passive immunization to block primary infection with **HIV**.

L4 ANSWER 15 OF 99 MEDLINE on STN
96401633. PubMed ID: 8926281. Comparison of cervicovaginal humoral immunity in clinically asymptomatic (CDC A1 and A2 category) patients with **HIV**-1 and **HIV**-2 infection. Belec L; Tevi-Benissan C; Dupre T; Mohamed A S; Prazuck T; Gilquin J; Kanga J M; Pillot J. (Unite d'Immunologie Microbienne, Institut Pasteur, Paris, France.) Journal of clinical immunology, **(1996 Jan)** 16 (1) 12-20. Journal code: 8102137. ISSN: 0271-9142. Pub. country: United States. Language: English.
AB Paired sera and cervicovaginal secretions (CVS) from 11 **HIV**-1- and 11 **HIV**-2-infected women, all clinically asymptomatic (CDC A1 and A2 categories), were analyzed for total IgG, **IgA**, albumin (HSA), IgG, and **IgA** antibodies to **env**-encoded surface glycoproteins of **HIV**-1 (**gp160**) and of **HIV**-2 (gp105), by comparison to 15 age-matched healthy controls. Secretion rates of IgG and **IgA** into CVS were evaluated by calculation of their relative coefficients of excretion (RCE) by reference to HSA. Cervicovaginal production of anti-**HIV** antibodies was evaluated by comparison between specific antibody activities of IgG and of **IgA** to **HIV** in CVS were, respectively, 6- and 4-fold increased, whereas the secretion rate of total IgG was 2.1-fold increased and that of total **IgA** was 2.5-fold reduced. In contrast, total IgG and **IgA** as well as their secretion rates were normal in **HIV**-2-infected women. In **HIV**-1- but not in **HIV**-2-infected women, HSA levels in cervicovaginal washings were twofold increased, demonstrating alteration of the **mucosal** barrier in **HIV**-1 infection. In **HIV**-1-infected patients, IgG and **IgA** to **gp160** were detected in all sera and CVS. In **HIV**-2-infected patients, IgG to gp105 was detected in all sera and CVS, whereas **IgA** to gp105 could be detected in only half of sera and one-third of CVS. Cross-reactivity by IgG and/or **IgA** to **HIV**-1 or **HIV**-2 against the surface glycoprotein of the other **HIV** type was observed in sera as well as in CVS, and more frequently in **HIV**-2- than in **HIV**-1-infected women. Finally, the mean specific activities of IgG and of **IgA** to **gp160** or gp105 were higher in CVS than in sera, evidencing a possible local synthesis of both isotypes in **HIV**-1 as well as in **HIV**-2 infections. As early as the asymptomatic stages, **HIV**-1 affects the cervicovaginal mucosa more than **HIV**-2 does, suggesting higher viral replication within the female genital tract in **HIV**-1 infection than in **HIV**-2 infection.

L4 ANSWER 16 OF 99 MEDLINE on STN
96363710. PubMed ID: 8719522. Construction and immunogenicity of Salmonella typhimurium vaccine vectors that express **HIV**-1 **gp120**. Fouts T R; Tuskan R G; Chada S; Hone D M; Lewis G K. (Department of Geographic Medicine, School of Medicine, University of Maryland at Baltimore 21201, USA.) Vaccine, **(1995 Dec)** 13 (17) 1697-705. Journal code: 8406899. ISSN: 0264-410X. Pub. country: ENGLAND: United Kingdom. Language: English.
AB Since the **human immunodeficiency virus** (**HIV**-1) is transmitted either parenterally or sexually, both **mucosal** and systemic immune responses may be required to provide protective immunity. Attenuated Salmonella vectors expressing heterologous antigen can stimulate responses in both compartments. To evaluate the utility of Salmonella vectors as an **HIV**-1 vector vaccine, a gene expression cassette encoding recombinant **HIV**-1 **gp120** (rgp120) was integrated into the hisOGD locus of Salmonella typhimurium aroA strain, SL3261 (SL3261::120). To test if increased antigen expression potentiates immunogenicity, strains were constructed that express rgp120 from a multicopy asd-stabilized plasmid (SL7207 pYA:120). Immunoblot analysis demonstrated that SL7207 pYA:120 expressed approximately 50-fold more rgp120 than SL3261::120. Oral immunization of BALB/c mice with these strains did not stimulate an **env**-specific CTL response or a significant rise in antigp120 antibody titer as compared to controls. However, splenic T cells from SL7207 pYA::120 immunized mice proliferated upon restimulation with **gp120** in vitro while splenocytes from SL3261::120 immunized mice did not, **gp120** restimulated splenic T cells from SL7207 pYA:120 immune mice also produced IFN-gamma but no IL-5. Two conclusions can be drawn from these results. First, high level expression of rgp120 in Salmonella vectors is necessary to stimulate a **gp120**-specific immune response in mice. Second, Salmonella::rgp120 stimulates a **gp120**-specific Th1 response in mice. This is the first report to describe the construction of a Salmonella::rgp120 vector vaccine that is immunogenic in mice.

L4 ANSWER 17 OF 99 MEDLINE on STN
96351473. PubMed ID: 8717405. Optimization of live oral Salmonella-**HIV**-1 vaccine vectors for the induction of **HIV**-specific **mucosal** and systemic immune responses. Hone D M; Wu S; Powell R J; Pascual D W; Van Cott J; McGhee J; Fouts T R; Tuskan R G; Lewis G K. (Vaccine Vector Group, School

of Medicine, University of Maryland at Baltimore, USA.) Journal of biotechnology, **(1996 Jan 26)** 44 (1-3) 203-7. Ref: 25. Journal code: 8411927. ISSN: 0168-1656. Pub. country: Netherlands. Language: English.

AB Recent evidence suggests that live oral Salmonella-**HIV** vaccine vectors have the potential to elicit **HIV**-specific T cell-mediated immunity in both the **mucosal** and systemic compartments. We are using the mouse-typhoid model to identify Salmonella::**HIV** vaccine vector constructs that elicit **HIV**-specific **mucosal** and systemic immune responses. Oral immunization of mice with a Salmonella strain that expresses recombinant **gp120** (rgp120) in the cytoplasm of the vector elicits a modest **gp120**-specific T cell proliferation response in the spleen. However, such Salmonella constructs did not stimulate the development of **gp120**-specific serum IgG or cytotoxic T lymphocytes (CTLs). Interestingly, the majority of cytoplasmically-expressed rgp120 forms inclusion bodies in Salmonella. We believe that in this form rgp120 is highly susceptible to protease degradation by the vector. As such, cytoplasmic rgp120 may not persist in the host after vaccination, resulting in the modest immunogenicity of rgp120 in these constructs. To circumvent this problem we constructed Salmonella strains that express rgp120 on the surface of the vector. Preliminary data suggest that surface-expressed rgp120 is significantly more immunogenic in both the **mucosal** and systemic compartments than cytoplasmic rgp120. These results, therefore, support the proposal that Salmonella vectors will be a safe and inexpensive means for delivery of **HIV** antigens to, and the elicitation of **HIV**-specific T cells in, the **mucosal** and systemic compartments.

L4 ANSWER 18 OF 99 MEDLINE on STN

96327872. PubMed ID: 8735090. Flow cytometric immunofluorescence assay for detection of antibodies to **human immunodeficiency virus** type 1 using insoluble precursor forms of recombinant polyproteins as carriers and antigens. Hu Y W; Birch P; Balaskas E; Zeibdawi A; Scalia V; Theriault-Valin S A; Gill P; Aye M T. (National Testing Laboratory, Canadian Red Cross Society, Ottawa, Ontario, Canada.) Journal of clinical microbiology, **(1996 Jun)** 34 (6) 1412-9. Journal code: 7505564. ISSN: 0095-1137. Pub. country: United States. Language: English.

AB A new serological assay, the recombinant flow cytometric immunofluorescence assay (r-FIFA), was developed for the early detection of **human immunodeficiency virus** type 1 (**HIV**-1) antibodies by using recombinant insoluble forms of **HIV**-1 Gag-p45, Gag-**gp41** chimeric protein, **gp160**, Pol97 polyprotein as antigens and autologous carriers through flow cytometry. These recombinant proteins were expressed in insect cells by a baculovirus expression system. Eight anti-**HIV**-1 seroconversion panels, a low-titer anti-**HIV**-1 panel from Boston Biomedica Inc. (BBI), and three **HIV**-1 seroconversion specimens from the Provincial Health Laboratory of Ontario, Toronto, Ontario, Canada (PHL), were tested and analyzed by r-FIFA. In sensitivity comparisons between r-FIFA and tests licensed by the U.S. Food and Drug Administration, which were used to test all of the **HIV**-1 panels from BBI, detection of **HIV**-1 antibody by r-FIFA was on average greater than 20 days earlier than that by enzyme immunoassay. The sensitivity of r-FIFA has permitted the detection of **HIV**-1-specific immunoglobulin G (IgG), IgM, and **IgA** antibodies during seroconversion. A kinetic analysis of **HIV**-1 antibody production of r-FIFA has shown that either IgG or IgM, or both, can be detected, depending on the phase and type of the immune response in the **HIV**-1-infected individual. Both primary and secondary immune responses were observed during this period. The r-FIFA results suggest that implementation of r-FIFA may significantly reduce the "window" period from the time of infection to the time of seroconversion, with earlier detection of antibodies after initial infection. This would also make it possible for us to understand the immune response and the precise mechanisms of immunopathogenesis in the early period of **HIV**-1 infection.

L4 ANSWER 19 OF 99 MEDLINE on STN

96268534. PubMed ID: 8846163. The role of Candida albicans secreted aspartic proteinase in the development of candidoses. Hoegl L; Ollert M; Korting H C. (Department of Dermatology, Ludwig-Maximilians-University, Munich, Germany.) Journal of molecular medicine (Berlin, Germany), **(1996 Mar)** 74 (3) 135-42. Ref: 71. Journal code: 9504370. ISSN: 0946-2716. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB Although Candida albicans infections in humans are increasingly frequent, our understanding of the host-parasite relationship is limited. The secreted aspartic proteinase of C. albicans was first described in 1965 and has proved to be a major factor in virulence. This enzyme belongs to the class of aspartic proteinases which includes pepsin and renin in humans. Although found in some fungi, secreted aspartic proteinase is rare in these organisms. While the existence of several isoenzymes may not be fully established, it is now obvious that at least seven different genes encode for secreted aspartic proteinase. Within Candida cells it is

located in membrane-bound vesicles. Upon fusion of these subcellular structures within the plasma membrane, the enzyme is released to the **environment**. In the context of human **mucosal** diseases it is responsible both for adhesion and invasion. Strains from **HIV**-infected patients with oral candidosis generally exhibit higher enzymatic activity than control strains. In future secreted aspartic proteinase may prove a prime target for new types of antimycotics.

L4 ANSWER 20 OF 99 MEDLINE on STN

96266328. PubMed ID: 8673922. Protective **mucosal** immunity elicited by targeted iliac lymph node immunization with a subunit SIV **envelope** and core vaccine in macaques. Lehner T; Wang Y; Cranage M; Bergmeier L A; Mitchell E; Tao L; Hall G; Dennis M; Cook N; Brookes R; Klavinskis L; Jones I; Doyle C; Ward R. (Department of Immunology, United Medical School, Guy's Hospital, London, UK.) Nature medicine, **(1996 Jul)** 2 (7) 767-75. Journal code: 9502015. ISSN: 1078-8956. Pub. country: United States. Language: English.

AB Prevention of sexually transmitted **HIV** infection was investigated in macaques by immunization with a recombinant SIV (simian immunodeficiency virus) **envelope** gp 120 and core p27 vaccine. In two independent series of experiments, we used the novel targeted iliac lymph node (TILN) route of immunization, aiming close to the iliac lymph nodes draining the genitorectal mucosa. Rectal challenge with the SIVmac 32H J5 molecular clone in two series induced total protection in four out of seven macaques immunized by TILN, compared with infection in 13 of 14 unimmunized macaques or immunized by other routes ($P = 0.025$). The remaining three macaques showed either a decrease in viral load (> 90%) or transient viremia, indicating that all seven TILN-immunized macaques showed total or partial protection ($P = 0.001$). Protection was associated with significant increase in the iliac lymph nodes of **IgA** antibody-secreting cells to p27 ($P < 0.02$), CD8-suppressor factor ($P < 0.01$), and the chemokines RANTES and MIP-1 beta ($P < 0.01$).

L4 ANSWER 21 OF 99 MEDLINE on STN

96264828. PubMed ID: 8701587. Immunization with a soluble recombinant **HIV** protein entrapped in biodegradable microparticles induces **HIV**-specific CD8+ cytotoxic T lymphocytes and CD4+ Th1 cells. Moore A; McGuirk P; Adams S; Jones W C; McGee J P; O'Hagan D T; Mills K H. (Biology Department, St. Patrick's College, Maynooth, Co. Kildare, Ireland.) Vaccine, **(1995 Dec)** 13 (18) 1741-9. Journal code: 8406899. ISSN: 0264-410X. Pub. country: ENGLAND: United Kingdom. Language: English.

AB One of the major obstacles to the development of successful recombinant vaccines against **human immunodeficiency virus** (**HIV**) and other intracellular pathogens is the identification of a safe and effective vaccine delivery system for the induction of cell mediated immunity with soluble protein antigens. In this study it was demonstrated that immunization with a recombinant **HIV envelop** (**env**) protein entrapped in biodegradable poly(lactide-co-glycolide) (PLG) microparticles induced consistent **HIV**-specific CD4+ and CD8+ T-cell responses in mice. Major histocompatibility complex (MHC) class I-restricted cytotoxic T lymphocytes (CTL) responses were detected following a single systemic immunization with **gp120** entrapped microparticles and when given by the intranasal (i.n.) route induced **HIV**-specific CD8+ CTL and secretory **IgA**. Furthermore immunization with **gp120** entrapped in microparticles generated CD4+ T cells that secreted moderate to high levels of IFN-gamma. Therefore, PLG microparticles are a safe and effective means of delivering antigen to the appropriate processing site for the generation of class I-restricted CTL, and are also capable of inducing Th1 cells.

L4 ANSWER 22 OF 99 MEDLINE on STN

96264725. PubMed ID: 8683152. **Mucosal** immunity to **HIV**-1: systemic and vaginal antibody responses after intranasal immunization with the **HIV**-1 C4/V3 peptide T1SP10 MN(A). Staats H F; Nichols W G; Palker T J. (Department of Medicine, Center for AIDS Research, Duke University Medical Center, Durham, NC 27710, USA.) Journal of immunology (Baltimore, Md. : 1950), **(1996 Jul 1)** 157 (1) 462-72. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB To optimize **mucosal** immune responses to the **HIV**-1 peptide vaccine candidate T1SP10 MN(A), we intranasally immunized BALB/c and C57BL/6 mice with C4/V3 **HIV**-1 peptide together with the **mucosal** adjuvant cholera toxin (CT). Four doses over a 4-wk period resulted in peak serum anti-peptide IgG titers of > 1:160,000 in BALB/c mice and > 1:520,000 in C57BL/6 mice, and significant levels (>1:30,000) persisted in both strains of mice for longer than 6 mo. Furthermore, intranasal immunization with peptide and CT induced serum IgG reactivity to **HIV**-1 **gp120** and **HIV**-1(MN) neutralizing responses. The primary anti-peptide IgG subclass was IgG1, suggesting a predominant Th2-type response. In addition to elevated serum anti-peptide A responses, intranasal immunization with T1SP10 MN(A) and CT induced both vaginal anti-peptide IgG and **IgA**

responses, which persisted for 91 days in both strains of mice. Vaginal anti-**HIV IgA** was frequently associated with secretory component, suggesting transepithelial transport of **IgA** into vaginal secretions. Cervical lymph nodes contained the highest relative concentration of anti-T1SP10 MN(A) IgG-producing cells, while the spleen was the next major site of anti-T1SP10 MN(A) IgG-producing cells. Ag-specific proliferative responses were also detected in cervical lymph node and spleen cell populations after intranasal immunization with T1SP10 MN(A) and CT. In addition, intranasal immunization with T1SP10 MN(A) and CT was able to induce anti-**HIV** cell-mediated immunity in vivo as indicated by the induction of delayed-type hypersensitivity. Therefore, intranasal immunization with hybrid **HIV** peptides provides a noninvasive route of immunization that induces both long-lived systemic and **mucosal** Ab responses as well as cell-mediated immunity to **HIV**.

L4 ANSWER 23 OF 99 MEDLINE on STN

96259174. PubMed ID: 8848337. Virus-induced immunosuppression is linked to rapidly fatal disease in infant rhesus macaques infected with simian immunodeficiency virus. Otsyula M G; Miller C J; Marthas M L; Van Rompay K K; Collins J R; Pedersen N C; McChesney M B. (School of Veterinary Medicine, University of California-Davis 95616-8542, USA.) Pediatric research, **(1996 Apr)** 39 (4 Pt 1) 630-5. Journal code: 0100714. ISSN: 0031-3998. Pub. country: United States. Language: English.

AB Six newborn rhesus macaques were experimentally infected with pathogenic Simian immunodeficiency virus of macaques (SIVmac251), and three newborn macaques were infected with avirulent SIVmac1A11. The former developed rapidly fatal simian AIDS and died within 26 wk of age, whereas the latter remained clinically normal. Infant monkeys that developed rapidly progressive disease had rapid declines in CD4+ cells and were unable to mount IgG and **IgA** antibody responses to SIV or to an unrelated antigen, tetanus toxoid. IgM antibody responses were near normal to both SIV-specific and nonspecific antigens. Cytotoxic T lymphocyte (CTL) responses to SIV **envelope** were observed in animals infected with either virulent or avirulent SIV. These studies demonstrated that virulent SIVmac infection induced a rapid immunosuppression that was both SIV-specific and nonspecific in nature. The observation that virulent strains of SIV can rapidly induce a global immunosuppression provides one explanation for the rapid disease course in some **HIV**-infected children and supports the strategy of early and vigorous antiviral drug therapy to alter the disease course even if this does not prevent infection.

L4 ANSWER 24 OF 99 MEDLINE on STN

96142210. PubMed ID: 8548327. **HIV gp120**-specific cell-mediated immune responses in mice after oral immunization with recombinant Salmonella. Berggren R E; Wunderlich A; Ziegler E; Schleicher M; Duke R C; Looney D; Fang F C. (Division of Infectious Diseases, University of Colorado Health Sciences Center, Denver 80267, USA.) Journal of acquired immune deficiency syndromes and human retrovirology : official publication of the International Retrovirology Association, **(1995 Dec 15)** 10 (5) 489-95. Journal code: 9501482. ISSN: 1077-9450. Pub. country: United States. Language: English.

AB Salmonella is of great interest as a potential **human immunodeficiency virus** vaccine vector because of its ability to elicit potent **mucosal** and systemic immune responses when administered orally. To determine whether such a vaccine could elicit an immune response in mice, plasmids expressing **HIV gp120**-LAI were introduced into attenuated S. typhimurium. Three serial doses of 10(10) recombinant organisms were administered orally to BALB/c mice at 2-week intervals. Immunized mice but not control mice demonstrated proliferative T cell responses to **gp120**-LAI, comparable in magnitude to the proliferative responses to Salmonella antigens. Immunized mice had detectable serum and intestinal Salmonella-specific **IgA** and serum Salmonella-specific IgG. However, no **gp120**-specific antibody was detected in either serum or intestinal washes. These results indicate that live recombinant Salmonella-based vaccine constructs can induce **HIV**-specific cellular immune responses in vivo.

L4 ANSWER 25 OF 99 MEDLINE on STN

96071531. PubMed ID: 7585151. Neutralization of **HIV**-1 by secretory **IgA** induced by oral immunization with a new macromolecular multicomponent peptide vaccine candidate. Bukawa H; Sekigawa K; Hamajima K; Fukushima J; Yamada Y; Kiyono H; Okuda K. (Department of Oral and Maxillofacial Surgery, Yokohama City University School of Medicine, Japan.) Nature medicine, **(1995 Jul)** 1 (7) 681-5. Journal code: 9502015. ISSN: 1078-8956. Pub. country: United States. Language: English.

AB Control of pandemic infection of **human immunodeficiency virus** type 1 (**HIV**-1) requires some means of developing **mucosal** immunity against **HIV**-1 because sexual transmission of the virus occurs mainly through the **mucosal** tissues. However, there is no evidence as yet that the

secretory immunoglobulin A (**IgA**) antibody induced by immunization with antigens in experimental animals can neutralize **HIV**-1. We demonstrate here that oral immunization with a new macromolecular peptide antigen and cholera toxin (CT) induces a high titre (1:2") of gut-associated and secretory **IgA** antibody to **HIV**-1. Using three different neutralizing assays, we clearly demonstrate that this secretory **IgA** antibody is able to neutralize **HIV**-1IIIB, **HIV**-1SF2 and **HIV**-1MN. Our new approach may prove to be important in the development of a **mucosal** vaccine that will provide protection of **mucosal** surfaces against **HIV**-1.

L4 ANSWER 26 OF 99 MEDLINE on STN

96065464. PubMed ID: 7483777. Construction and characterization of a Salmonella typhi-based **human immunodeficiency virus** type 1 vector vaccine. Fouts T R; Lewis G K; Hone D M. (Department of Geographic Medicine, School of Medicine, University of Maryland at Baltimore 21201, USA.) Vaccine, **(1995 Apr)** 13 (6) 561-9. Journal code: 8406899. ISSN: 0264-410X. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Since the **human immunodeficiency virus** type 1 (**HIV**-1) is transmitted either parenterally or sexually, both systemic and **mucosal** immune responses might be required to provide protective immunity. One option is to express **HIV** proteins in attenuated Salmonella vectors that elicit immune responses in both compartments. The first step to constructing such a strain was achieved by integrating a gene expression cassette encoding recombinant **HIV**-1 **gp120** (rgp120) into the aroC locus of an attenuated vaccine strain of S. typhi. This rgp120 expression cassette utilizes the strong constitutive promoter, P1pp/lacUV5, and produces rgp120 to 0.05-01% of the total bacterial cell protein. Immunoblot analysis shows that the S. typhi strains containing the integrated cassette express a protein that is both recognized by anti-**gp120** monoclonal antibodies (mAbs) and is the appropriate size for nonglycosylated full-length **gp120** (52 kDa). Immunoblot analysis also demonstrates that the recombinant S. typhi strains express the rgp120 as monomers and multimers found predominantly in the insoluble fraction of the bacteria. Antigen-capture ELISA, using antibodies specific for continuous epitopes on **gp120**, revealed that the exposure of these epitopes on S. typhi-expressed rgp120 differs from exposure of these epitopes on baculovirus-expressed rgp120 that binds CD4. Epitopes in the first conserved region (109-113) and the third conserved/fourth variable regions (376-380, 382-384, 395-400) are more "surface-exposed", while one epitope in the third variable region (313-324) is more "buried" relative to the corresponding epitopes of baculovirus expressed **gp120**. Antibodies recognizing discontinuous epitopes of the CD4 binding domain do not react with the S. typhi expressed rgp120.(ABSTRACT TRUNCATED AT 250 WORDS)

L4 ANSWER 27 OF 99 MEDLINE on STN

96035231. PubMed ID: 7546413. Virus-specific antibody production and polyclonal B-cell activation in the intestinal mucosa of **HIV**-infected individuals. Eriksson K; Kilander A; Hagberg L; Norkrans G; Holmgren J; Czerkinsky C. (Department of Medical Microbiology and Immunology, University of Goteborg, Sweden.) AIDS (London, England), **(1995 Jul)** 9 (7) 695-700. Journal code: 8710219. ISSN: 0269-9370. Pub. country: United States. Language: English.

AB OBJECTIVE: To examine possible changes in **mucosal** B-cell activation status. DESIGN: To examine the frequency and isotype distribution of total and **HIV**-specific antibody-secreting cells (ASC) in the intestinal mucosa of **HIV**-infected individuals. METHODS: **Mucosal** lymphocytes were obtained by enzymatic treatment of duodenal pinch biopsies and the numbers of ASC were assayed with the enzyme-linked immunospot technique. RESULTS: High numbers of **HIV**-specific ASC were found in the intestine of all **HIV**-infected individuals despite low levels of **HIV**-specific blood ASC. All **HIV**-infected individuals had large numbers of intestinal immunoglobulin (Ig) A-ASC against the **HIV envelope** glycoprotein **gp160**. Eight out of nine patients also had **HIV gp160**-specific intestinal IgG-ASC. These **HIV**-specific ASC were detected irrespective of disease stage, route of infection, or levels of circulating CD4+ T cells. **HIV**-specific ASC were found in peripheral blood from patients with CD4+ T cells > or = 100 x 10(6)/l blood, but in none of three patients with low CD4+ T-cell counts. The frequencies of virus-specific ASC in the blood were on average 100-fold lower than that observed within the intestinal mucosa. **Mucosal** polyclonal B-cell activation was evident in **HIV**-infected individuals, as documented by significantly elevated numbers of Ig-secreting cells (ISC) in all three major Ig classes; on average, seven-, five- and 20-fold numbers of **IgA**, IgG and IgM-ISC compared with healthy controls. Furthermore, substantial numbers of ASC reacting with unrelated antigens such as dog albumin and keyhole limpet haemocyanin were detected in **HIV**-infected patients. Interestingly, patients with CD4+ T cells < 100 x 10(6)/l blood displayed large numbers of **HIV**-specific intestinal ASC even though total numbers of ISC,

including ASC reactive to unrelated antigens, were decreased. CONCLUSIONS: The large numbers of virus-specific ASC found in the intestine of **HIV**-infected individuals may be a consequence of local replication of **HIV**-1 resulting in a continuous antigen stimulation. The persistence of strong intestinal anti-**HIV** responses even at late stages of disease suggest that the **mucosal** B-cell responses are functionally intact throughout the disease. Furthermore, these results suggest that there is no correlation between **HIV**-specific ASC numbers and polyclonal B-cell activation. These observations indicate that intestinal B-cell activation is profoundly disregulated in **HIV**-infected individuals.

L4 ANSWER 28 OF 99 MEDLINE on STN

96013760. PubMed ID: 7474077. **Mucosal** model of immunization against **human immunodeficiency virus** type 1 with a chimeric influenza virus. Muster T; Ferko B; Klima A; Purtscher M; Trkola A; Schulz P; Grassauer A; Engelhardt O G; Garcia-Sastre A; Palese P; +. (Institut fur Angewandte Mikrobiologie, Universitat fur Bodenkultur, Vienna, Austria.) Journal of virology, **(1995 Nov)** 69 (11) 6678-86. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Previously, we constructed a chimeric influenza virus that expresses the highly conserved amino acid sequence ELDKWA of **gp41** of **human immunodeficiency virus** type 1 (**HIV**-1). Antisera elicited in mice by infection with this chimeric virus showed neutralizing activity against distantly related **HIV**-1 isolates (T. Muster, R. Guinea, A. Trkola, M. Purtscher, A. Klima, F. Steindl, P. Palese, and H. Katinger, J. Virol. 68:4031-4034, 1994). In the present study, we demonstrated that intranasal immunizations with this chimeric virus are also able to induce a humoral immune response at the **mucosal** level. The immunized mice had ELDKWA-specific immunoglobulins A in respiratory, intestinal, and vaginal secretions. Sustained levels of these secretory immunoglobulins A were detectable for more than 1 year after immunization. The results show that influenza virus can be used to efficiently induce secretory antibodies against antigens from foreign pathogens. Since long-lasting **mucosal** immunity in the genital and intestinal tracts might be essential for protective immunity against **HIV**-1, influenza virus appears to be a promising vector for **HIV**-1-derived immunogens.

L4 ANSWER 29 OF 99 MEDLINE on STN

95381933. PubMed ID: 7653407. IgG2 associated hypergammaglobulinaemia in some Nigerians with **HIV** infection. Uko G P; Griffiths M; Dawkins R L; Cobain T; Mohammed I; Hedo C; Okafor G; Umotong A B. (National Institute for Medical Research, Lagos, Nigeria.) African journal of medicine and medical sciences, **(1994 Dec)** 23 (4) 385-9. Journal code: 7801013. ISSN: 0309-3913.
Report No.: PIP-111459; POP-00255473. Pub. country: Nigeria. Language: English.

AB Concentrations of immunoglobulins (**IgA**, IgG and IgM) were measured in Nigerians with (**HIV**) infection. Considerable elevations up to two-fold the reference values were observed for IgG and IgM in the patient group as a whole but elevations in **IgA** concentration were least marked albeit significantly different from the healthy subjects. Elevation of a particular isotype was not always concomitant with elevation of the other major classes in the same patient. Overall, these elevations were observed in both symptomatic and asymptomatic infected subjects. Further analysis of IgG hyperglobulinemia showed that increases in this major class may be due to increased IgG2 subclass concentrations. It is suggested that elevation of IgG2 subclass in Nigerians with **HIV** infection and not IgG1 or IgG3 may be due to genetic and **environmental** factors rather than variation in the strain of the virus. The major and subclass concentrations of immunoglobulins were examined in 27 Nigerians with **HIV** infection. 12 had definite **HIV**-1 infection, 2 had both **HIV**-1 and **HIV**-2, and the remaining 15 were included because of the reactivity of their sera. The reference group was drawn from four major Nigerian population groups that were part of a group of 238 healthy Nigerians. Individual increases in IgM and IgG concentrations in the patient group varied and was sometimes up to 7-fold above the mean of those in the control group. Overall, the increases were about twice the mean concentrations found in the reference group. The IgM concentration range was 0.6-9.7 g/l in the **HIV** group (n = 27) vs. 0.4-4.6 in the reference group (n = 157, p 0.02). The IgG concentration range was 10-70 g/l in the **HIV** group (n = 27) vs. 10-30 g/l in the reference group (n = 160, p .001). The highest IgG concentrations in cases were found in symptomatic patients, but this relationship was not observed for IgM and **IgA**. The scattergram of **IgA** concentrations was the least elevated. The increase was significant when those with **HIV**-1 infection alone were compared with the healthy subjects (p .05). IgG2 subclass concentrations were determined only in patients of Kanuri and Hausa populations. In comparison to their healthy counterparts, IgG2 concentrations were significantly higher in the patient group (p .001). Other IgG subclasses

showed a bimodal distribution in both groups. There was no significant difference in distribution of IgG1, IgG3, and IgG4 concentrations between the reference and the **HIV** groups. In several ethnic groups polyclonal hypergammaglobulinemia has been reported to be a frequent feature of **HIV** infection with markedly increased **IgA** concentrations. The differences observed here do not reflect a variation in the strain of the virus in the Nigerian populations, but may be related to racial and **environmental** factors.

L4 ANSWER 30 OF 99 MEDLINE on STN
95351033. PubMed ID: 7625118. **HIV**-1 recombinant **gp160** vaccine induced antibodies in serum and saliva. The NIAID AIDS Vaccine Clinical Trials Network. Gorse G J; Rogers J H; Perry J E; Newman F K; Frey S E; Patel G B; Belshe R B. (Division of Infectious Diseases, Saint Louis University Health Sciences Center, MO 63110-0250, USA.) Vaccine, **(1995 Feb)** 13 (2) 209-14. Journal code: 8406899. ISSN: 0264-410X. Pub. country: ENGLAND: United Kingdom. Language: English.
AB As part of a phase I safety and immunogenicity trial of a vaccinia-expressed **HIV**-1 recombinant **gp160** (rgp160) candidate vaccine, we measured serum and saliva antibody responses in low risk, uninfected volunteers. Six healthy adult volunteers received 50 micrograms doses of rgp160 vaccine adjuvanted in alum and deoxycholate at months 0, 1, 6, and 12. A 200 micrograms rgp160 immunization was given to four volunteers at 18 months. The vaccine induced anti-**envelope** glycoprotein IgG and **IgA** serum antibodies in all six volunteers. Saliva antibodies to **envelope** glycoprotein appeared in some volunteers at certain timepoints. Three volunteers appeared to transiently develop vaccine-induced secretory **IgA** antibody to **envelope** glycoprotein in whole saliva.

L4 ANSWER 31 OF 99 MEDLINE on STN
95347060. PubMed ID: 7621578. Decreased cervicovaginal production of both IgA1 and IgA2 subclasses in women with AIDS. Belec L; Meillet D; Gaillard O; Prazuck T; Michel E; Ngondi Ekome J; Pillot J. (Unite d'Immunologie Microbienne, Institut Pasteur, Paris, France.) Clinical and experimental immunology, **(1995 Jul)** 101 (1) 100-6. Journal code: 0057202. ISSN: 0009-9104. Pub. country: ENGLAND: United Kingdom. Language: English.
AB Paired sera and cervicovaginal secretions from 35 **HIV**-1-infected women representing different CDC stages of **HIV** infection were evaluated for total **IgA**, IgA1 and IgA2, for **IgA**, IgA1 and IgA2 to **gp160**, and for albumin. Age-matched healthy women (n = 45) served as controls. The secretion rates of total **IgA**, IgA1 and IgA2 were evaluated by calculating their relative coefficients of excretion by reference to albumin. In **HIV**-infected women, total IgA1 and IgA2 in sera and in cervicovaginal secretions increased proportionately as early as stages II + III and more markedly at stage IV. By contrast, the secretion rates of total **IgA** IgA1 and IgA2 were markedly reduced in AIDS women, the IgA2 secretion rate decreasing significantly as early as stages II + III. This apparent discrepancy was probably the result of increased transudation of serum-borne immunoglobulins into the vaginal cavity, since albumin levels in cervicovaginal secretions increased significantly according to the stages of disease. **HIV**-reactive **IgA** antibodies in serum, as in cervicovaginal secretions, were principally found within the IgA1 subclass. In women at stage IV, a high local production of IgA1 to **gp160** occurred in spite of the impairment of cervicovaginal **IgA** synthesis, probably because of marked genital **HIV** replication at advanced stages.

L4 ANSWER 32 OF 99 MEDLINE on STN
95285607. PubMed ID: 7768037. Autoreactivity in **HIV**-1 infection: the role of molecular mimicry. Silvestris F; Williams R C Jr; Dammacco F. (Department of Biomedical Sciences and Human Oncology, University of Bari, Italy.) Clinical immunology and immunopathology, **(1995 Jun)** 75 (3) 197-205. Ref: 59. Journal code: 0356637. ISSN: 0090-1229. Pub. country: United States. Language: English.
AB Autoimmunity during **HIV**-1 infection may contribute to the immunopathogenesis of AIDS. Titers of autoantibodies to HLA molecules and other surface markers of CD4+ T cells appear to increase with the progression of disease and may correlate with lymphopenia. Other autoantibodies are directed at a number of regulatory molecules of the immune system. Genesis of autoreactivity may be related to structural homologies of **HIV**-1 **env**-products to such functional molecules involved in the control of self-tolerance. The most impressive similarities include the HLA-DR4 and DR2, the variable regions of TCR alpha-, beta-, and gamma-chain, the Fas protein, and several functional domains of IgG and **IgA**. Thus, **HIV**-1 infection may induce dysregulation leading to autoimmune response, through a number of molecular mimicry mechanisms. Pathogenicity of antibodies to T cells could also include the activation of membrane-to-nucleus signal transducers resulting in increased apoptosis. The evolution of autoimmune mechanisms during **HIV**-1

infection cannot exclude, however, progression to immunoproliferative malignancy, since aspects of oligoclonal immune response to **HIV**-1 components may occur in several autoimmune diseases which in some instances evolve to lymphoma.

L4 ANSWER 33 OF 99 MEDLINE on STN

95275458. PubMed ID: 7755912. Safety and immunogenicity of a V3 loop synthetic peptide conjugated to purified protein derivative in **HIV**-seronegative volunteers. Rubinstein A; Goldstein H; Pettoello-Mantovani M; Mizrachi Y; Bloom B R; Furer E; Althaus B; Que J U; Hasler T; Cryz S J. (Albert Einstein College of Medicine, Bronx, New York 10461, USA.) AIDS (London, England), **(1995 Mar)** 9 (3) 243-51. Journal code: 8710219. ISSN: 0269-9370. Pub. country: United States. Language: English.

AB OBJECTIVES: To develop a peptide-based model for a preventive vaccine for **HIV**-1 infection. DESIGN: Phase I trial in **HIV**-1-seronegative volunteers. PARTICIPANTS: Adult healthy subjects **HIV**-1-antibody-seronegative in an enzyme-linked immunosorbent assay, screened for tuberculin [purified protein derivative (PPD)] reactivity with 2 tuberculin units PPD-administered intradermally. INTERVENTIONS: Submicrogram doses of a PPD conjugate with a peptide of the primary neutralizing domain (PND) of **HIV**-1MN (PPD-MN-PND) were administered intradermally to tuberculin skin-test-positive and -negative volunteers. RESULTS: Antibodies to the MN-PND were measured after two immunizations in 10 out of 11 PPD skin-test-positive volunteers. After the fourth immunization high-affinity antibodies were detected, which persisted for over 1 year. High titers of MN-PND-specific immunoglobulin (Ig) G and **IgA** were detected in the serum and saliva of all volunteers tested. Serum antibodies were cross-reactive with PND peptide from some other **HIV**-1 strains but neutralized only the **HIV**-1MN prototype. Human leukocyte antigen (HLA)-B7-restricted MN-PND-specific cytotoxic T lymphocytes (CTL) were also detected. CONCLUSIONS: The PPD-MN-PND vaccine at submicrogram doses is safe and immunogenic in PPD skin-test-positive healthy adult volunteers. Long lasting humoral immune responses in the serum and saliva were possibly accompanied by HLA-B7-restricted CTL responses. This is a vaccine prototype that can be rapidly and inexpensively modified to include other peptide epitopes. It is especially suitable for use in a worldwide multibillion Bacillus Calmette-Guerin (BCG)-primed or tuberculosis-exposed population at risk for **HIV**-1 infection.

L4 ANSWER 34 OF 99 MEDLINE on STN

95237835. PubMed ID: 7721293. Soap and water prophylaxis for limiting genital ulcer disease and **HIV**-1 infection in men in sub-Saharan Africa. O'Farrell N. (Department of Genito-urinary Medicine, Guy's Hospitals, London, UK.) Genitourinary medicine, **(1993 Aug)** 69 (4) 297-300. Ref: 32. Journal code: 8503853. ISSN: 0266-4348.
Report No.: PIP-105610; POP-00272740. Pub. country: ENGLAND: United Kingdom. Language: English.

AB In general, East, Central and Southern Africa appear to be worse affected by **HIV**-1 infection than West Africa. So far there is little evidence to suggest that differences in either sexual behaviour or numbers of sexual partners could account for this disparity. Two risk factors in men for acquiring **HIV**-1, that tend to vary along this geographical divide, are lack of circumcision and genital ulcer disease (GUD) which are much less common in West Africa. Although uncircumcised men with GUD are an important high frequency **HIV**-1 transmitter core group, few interventions have targeted such individuals. Given the recent expansion in AIDS-related technologies, is it possible that methods effective in limiting GUD in the preantibiotic era have been overlooked? During the first and second world wars, chancroid, the commonest cause of GUD in Africa today, was controlled successfully with various prophylactics including soap and water. Many parts of Africa are undergoing social upheaval against a background of violence, and in this **environment** soap and water prophylaxis would now seem to merit re-evaluation as an intervention for preventing both GUD and **HIV**-1 in uncircumcised men. By facilitating healing of traumatic, inflammatory and infected penile lesions, pre- and post-exposure prophylaxis with soap and water could be a cheap and effective method for decreasing the risks of acquiring GUD and **HIV** in this vulnerable group of uncircumcised men. The heterosexual transmission of **HIV**-1 is highly efficient in sub-Saharan Africa. Being uncircumcised and having genital ulcer disease (GUD) are two factors which put men at risk for acquiring infection with **HIV**-1. In turn, uncircumcised men with GUD are an important high frequency **HIV**-1 transmitter core group. While the pathogenesis of GUD remains unclear, it probably requires an initial minor abrasion of normal skin, common among uncircumcised men with poor genital hygiene and areas of **mucosal** discontinuity on the penis. The moist **environment** under the foreskin hinders the rapid healing of subpreputial abrasions and also provides a

fine receptacle for the retention of sexually transmitted pathogens. Damage to the superficial subpreputial mucosa, which may be exacerbated if traumatized during sexual intercourse, forms a highly plausible entry point for **HIV**-1. Chancroid, the most common cause of GUD in Africa, was successfully controlled with a range of prophylactics during the first and second world wars, including basic hygiene using soap and water. Washing of the penis with soap and water should again be considered as a means of preventing both GUD and **HIV**-1 in uncircumcised men. By facilitating the healing of traumatic, inflammatory, and infected penile lesions, pre- and post-exposure prophylaxis with soap and water could be a cheap and effective method for decreasing the risk of acquiring GUD and **HIV** in such men.

L4 ANSWER 35 OF 99 MEDLINE on STN

95224394. PubMed ID: 7709073. Rapid and constant detection of **HIV** antibody response in saliva of **HIV**-infected patients; selective distribution of anti-**HIV** activity in the IgG isotype. Lu X S; Delfraissy J F; Grangeot-Keros L; Rannou M T; Pillot J. (Service de Microbiologie et d'Immunologie, Hopital Antoine Beclere, Clamart, France.) Research in virology, **(1994 Nov-Dec)** 145 (6) 369-77. Journal code: 8907469. ISSN: 0923-2516. Pub. country: France. Language: English.

AB Anti-**HIV** antibodies can be specifically detected with a sensitivity and a specificity of 100% in the saliva of all **HIV**-infected patients. A saliva collection device facilitates the sampling procedure, and if a rapid test is used, the diagnosis of infection can be established in as little as 10 min. The analysis of a group of CDC stage IV AIDS patients showed a decrease in lactoferrin (produced by the oral mucosa) in comparison with **HIV**-negative controls, associated with an increase in albumin (filtering from plasma), indicating an alteration of the **mucosal** barrier. The salivary anti-**HIV-gp160** activity was largely carried by the IgG isotype whereas the salivary antibacterial activity (anti-Streptococcus sobrinus; anti-LPS from Escherichia coli) remained located in the **IgA** isotype as usually observed with all infectious agents. Salivary IgG carried a specific anti-**gp160** activity 25-fold higher than that of serum IgG. Thus, significant local synthesis of specific IgG by oral mucosa was revealed as a characteristic of **HIV** infection.

L4 ANSWER 36 OF 99 MEDLINE on STN

95221983. PubMed ID: 7706805. **Human immunodeficiency virus** type 1 **env** and p17gag sequence variation in polymerase chain reaction-positive, seronegative injection drug users. Markham R B; Yu X; Farzadegan H; Ray S C; Vlahov D. (Department of Molecular Microbiology and Immunology, Johns Hopkins School of Hygiene and Public Health, Baltimore, Maryland 21205.) Journal of infectious diseases, **(1995 Apr)** 171 (4) 797-804. Journal code: 0413675. ISSN: 0022-1899. Pub. country: United States. Language: English.

AB Variation in gene sequences from **human immunodeficiency virus** type 1 (**HIV**-1) p17gag and the third hypervariable region (V3 loop) of **env** was examined in a cross-sectional study of single specimens from 4 **HIV**-1 polymerase chain reaction-positive, seronegative injection drug users. As observed in sexually transmitted disease, clones of **HIV**-1 genes isolated from an individual were remarkably homogeneous, with amino acid variation in the **envelope** region of 0.3%-0.9% and in p17gag of 0.0%-0.7%. Intersubject variation was much greater (at the amino acid level, 15% for the **envelope** and 4.3% for p17gag), with conservation in the **envelope** only of regions at the base of the V3 loop. Since at least some subjects likely acquired infection intravenously, the ability of virus to survive in seminal fluid or on **mucosal** surfaces cannot explain the observed homogeneity, which may depend on direct interactions between the virus and the infected cell.

L4 ANSWER 37 OF 99 MEDLINE on STN

95194704. PubMed ID: 7888199. Immunogenicity of recombinant adenovirus-**human immunodeficiency virus** vaccines in chimpanzees following intranasal administration. Lubeck M D; Natuk R J; Chengalvala M; Chanda P K; Murthy K K; Murthy S; Mizutani S; Lee S G; Wade M S; Bhat B M; +. (Department of Biotechnology and Microbiology, Wyeth-Ayerst Research, Radner, Pennsylvania 19087.) AIDS research and human retroviruses, **(1994 Nov)** 10 (11) 1443-9. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.

AB Recombinant adenovirus (Ad)-**human immunodeficiency virus** (**HIV**) vaccines expressing HIVIIIB **Env** and Gag proteins were evaluated for immunogenicity in chimpanzees following intranasal administration. When Ad7-, Ad4-, and Ad5-vectored vaccines were administered sequentially at 0, 24, and 52 weeks, respectively, to three chimpanzees, the inoculations resulted in limited virus replication in the nasopharynx, but extensive Ad-**HIV** replication occurred in the intestine. High-titered IgG serum antibody responses to **Env** and Gag that were nonneutralizing were induced

following booster administration of Ad4-**HIV** recombinant viruses. Following the Ad5-**HIV** booster, low levels of neutralizing antibodies as well as V3 loop antibodies were induced in all three chimpanzees that persisted for several months. Administration of a **gp160** subunit vaccine (baculovirus derived) in SAF-m 24 weeks later boosted broadly neutralizing serum antibodies that peaked within 1 month of the injection. Two additional subunit boosters 19 and 37 weeks later were progressively less effective at stimulating serum neutralizing antibody responses. Substantial local immune responses were induced in nasal, vaginal, and salivary secretions following the third Ad-**HIV** intranasal immunization. These responses were further boosted with the **gp160** subunit vaccine, which also stimulated production of rectal antibodies. The predominant responses in all secretions tested were of the IgG isotype, although some **IgA** responses were also detected. Strong blastogenic responses to **HIV** recombinant **Env** and Gag proteins were induced after each immunization.

L4 ANSWER 38 OF 99 MEDLINE on STN

95169516. PubMed ID: 7865335. New approaches for **mucosal** vaccines for AIDS: encapsidation and serial passages of poliovirus replicons that express **HIV**-1 proteins on infection. Morrow C D; Porter D C; Ansardi D C; Moldoveanu Z; Fultz P N. (Department of Microbiology, University of Alamaba at Birmingham 35294.) AIDS research and human retroviruses, **(1994)** 10 Suppl 2 S61-6. Ref: 37. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.

AB It is apparent that a safe and effective **HIV** vaccine is an important component in the development of rational approaches for the control and prevention of **HIV** transmission. Given the fact that the virus most often encounters a **mucosal** surface during sexual transmission, a vaccine designed to stimulate both the systemic and **mucosal** immune systems is essential. Poliovirus is attractive as a delivery system because of several biological features inherent to the virus. First, the pathogenesis of the virus has been well studied, and important features have been identified. The virus is naturally transmitted by a fecal-oral route and is stable in the harsh conditions of the gastrointestinal tract. Second, previous studies using attenuated vaccine strains of poliovirus showed that a long-lasting systemic and **mucosal** immunity is generated after administration of the vaccines. Studies have demonstrated the presence of circulating T cells that proliferate to whole inactive poliovirus or peptides corresponding to amino acids of the VP1 proteins in previously immunized individuals. These results established that immunization with poliovirus stimulates both the humoral and cell-mediated components of the immune system. Third, the attenuated strains of poliovirus are safe for humans and are given to infants as early as 6 months of age. The incorporation of foreign genes into the attenuated strains would be an attractive feature that should pose no more of a health risk than that associated with administration of the attenuated vaccines. Finally, studies from this laboratory, as well as others, have established the feasibility of incorporating foreign genes into the poliovirus cDNA.(ABSTRACT TRUNCATED AT 250 WORDS)

L4 ANSWER 39 OF 99 MEDLINE on STN

95145526. PubMed ID: 7531144. Recombinant CD4-IgE, a novel hybrid molecule, inducing basophils to respond to **human immunodeficiency virus** (**HIV**) and **HIV**-infected target cells. Krauss S; Kufer P; Federle C; Tabaszewski P; Weiss E; Rieber E P; Riethmuller G. (Institute for Immunology, University of Munich, Germany.) European journal of immunology, **(1995 Jan)** 25 (1) 192-9. Journal code: 1273201. ISSN: 0014-2980. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB Basophils and mast cells, as the main effector cells in IgE-mediated type I hypersensitivity, are involved in the elimination of parasites and, according to recent findings, may also play an important role in the defense against bacterial and viral infections. Using a genetic engineering approach we wanted to redirect this potent IgE-mediated defense system against intruding human immune deficiency virus. We constructed a recombinant CD4-IgE molecule, consisting of the two N-terminal domains of CD4 and the CH2-4 domains of the IgE heavy chain, thus providing the IgE with specificity for the **gp120** of **human immunodeficiency virus** (**HIV**). The binding properties of hybrid CD4-IgE to the high-affinity receptor for IgE (Fc epsilon RI) on basophils as well as to the low-affinity receptor (Fc epsilon RII or CD23) for IgE on lymphoid cells were found to be similar to those of native IgE. At the same time, the CD4 domains of the recombinant molecule retained the **gp120** binding specificity with an affinity similar to that of the native CD4. By functional tests, we demonstrated that CD4-IgE armed basophils can be triggered by free **HIV** and by **HIV**-infected cells to release their mediators. We further show that **HIV**-triggered basophils lead to a decreased replication of **HIV** in susceptible T cells. We, therefore, conclude that the type I hypersensitivity effector cells can be engaged in

the elimination of **HIV**-infected cells, at least in vitro. Because of the strong binding of the CD4-IgE construct to the Fc epsilon RI, we assume that CD4-IgE has a short t1/2 in serum, but may similarly to IgE exhibit prolonged resident time on basophils and mast cells, which are located close to **mucosal** surfaces or in the connective tissue. Thus CD4-IgE could play an important role in the elimination of **HIV** also in vivo.

L4 ANSWER 40 OF 99 MEDLINE on STN

95133350. PubMed ID: 7831961. Physical contact with lymphocytes is required for reactivation of dormant **HIV**-1 in colonic epithelial cells: involvement of the **HIV**-1 LTR. Faure E; Yahi N; Zider A; Cavard C; Champion S; Fantini J. (Institut de Chimie Biologique, Universite de Provence, Marseille, France.) Virus research, **(1994 Oct)** 34 (1) 1-13. Journal code: 8410979. ISSN: 0168-1702. Pub. country: Netherlands. Language: English.

AB **HIV**-1 transmission from **mucosal** epithelial cells to lymphocytes is a potential mechanism of **HIV**-1 contamination during sexual intercourse. The human colon epithelial cell line HT-29, that is infectable by various **HIV**-1 strains, is a useful model for studying the molecular mechanisms involved in this process. In the present study, we show that HT-29 cells, when exposed to either **HIV**-1(LAI) or **HIV**-1(NDK) at a low multiplicity of infection, became infected but did not produce infectious virions. Using two-compartment cell culture chambers separated by a porous membrane, we showed that PBL were able to rescue infectious **HIV**-1 from latently infected HT-29 cells following a physical interaction between the two cell populations. In contrast, HT-29 cells, infected with the same viruses at a high multiplicity of infection, were able to produce mature viral particles that were infectious to PBL in absence of cellular contacts. Transient expression assays using an indicator gene under the control of the **HIV**-1 long terminal repeat revealed that cell-to-cell contact induced an activation of the **HIV**-1 promoter. These observations provide a putative molecular mechanism for transmission of **HIV**-1 from **mucosal** epithelial cells to lymphocytes.

L4 ANSWER 41 OF 99 MEDLINE on STN

95108957. PubMed ID: 7809997. Submicroscopic profile of Isospora belli enteritis in a patient with acquired immune deficiency syndrome. Comin C E; Santucci M. (Institute of Anatomic Pathology, University of Florence Medical School, Italy.) Ultrastructural pathology, **(1994 Sep-Oct)** 18 (5) 473-82. Journal code: 8002867. ISSN: 0191-3123. Pub. country: United States. Language: English.

AB Small bowel **mucosal** fragments from a **human immunodeficiency virus**-positive female patient with chronic diarrhea were investigated by transmission electron microscopy, and Isospora belli enteritis was documented. The submicroscopic profile was characterized by a moderate abnormality of **mucosal** architecture with reduction in height of villi and hypertrophy of crypts. Stages of both asexual (trophozoite, schizont and merozoite) and sexual (macrogametocyte) phases of the life cycle of the parasite were identified in the epithelium, always enclosed within a parasitophorous vacuole. Moreover, the presence of occasional extracellular merozoites in the intestinal lumen and in the lamina propria near or within lymphatic vessels was documented. These findings expand the current knowledge of this parasite regarding its capacity to survive in an extracellular **environment** and document a possible mechanism by which extraintestinal infection can take place.

L4 ANSWER 42 OF 99 MEDLINE on STN

95107997. PubMed ID: 7809077. Infection of vaginal and colonic epithelial cells by the **human immunodeficiency virus** type 1 is neutralized by antibodies raised against conserved epitopes in the **envelope** glycoprotein **gp120**. Furuta Y; Eriksson K; Svennerholm B; Fredman P; Horal P; Jeansson S; Vahlne A; Holmgren J; Czerkinsky C. (Department of Clinical Virology, Goteborg University, Sweden.) Proceedings of the National Academy of Sciences of the United States of America, **(1994 Dec 20)** 91 (26) 12559-63. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB The rectal and genital tract mucosae are considered to be major sites of entry for the **human immunodeficiency virus** (**HIV**) during sexual contact. We now demonstrate that vaginal epithelial cells can be infected by **HIV** type 1 (**HIV**-1) via a mechanism similar to that described for neuroglial cells and, more recently, for colorectal epithelial cells, involving initial interaction of the **HIV**-1 **envelope** glycoprotein **gp120** with a cell-surface glycosphingolipid (sulfated lactosylceramide). A hyperimmune serum against **gp120** was able to neutralize **HIV**-1 infection of vaginal epithelial cells. Site-directed immunization was employed to identify sites on **gp120** recognized by antibodies neutralizing **HIV**-1 infection of vaginal and colonic epithelial cells. Hyperimmune sera were raised in monkeys against a series of 40 overlapping

synthetic peptides covering the entire sequence of **HIV**-1 (HTLV-IIIB) **gp120**. Antisera raised against five synthetic peptides, corresponding to three relatively conserved regions and to the hypervariable region (V3 loop), efficiently neutralized **HIV**-1 infection of human vaginal epithelial cells in vitro. Similar results were obtained with the colonic cells. Hyperimmune sera to all five peptides have been shown earlier to neutralize **HIV**-1 infectivity in CD4+ T cells. These results have obvious implications for the design of **mucosal** subunit vaccines against sexually transmitted **HIV**-1 infections.

L4 ANSWER 43 OF 99 MEDLINE on STN
95106017. PubMed ID: 7807285. Diagnosis and prediction of pediatric **HIV**-1 infection and AIDS: current status. Ugen K E; Von Feldt J M; Weiner D B; Ziegner U H. (Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia.) Journal of clinical laboratory analysis, **(1994)** 8 (5) 309-14. Ref: 43. Journal code: 8801384. ISSN: 0887-8013. Pub. country: United States. Language: English.
AB The increase in the incidence of **HIV**-1 infection in women of child bearing age has resulted in a surge in the number of cases of pediatric AIDS. The World Health Organization (WHO) has estimated that the number of cases of pediatric AIDS worldwide will be at least 10 million by the year 2000. This alarming statistic underscores the need for accurate prediction and diagnosis of pediatric **HIV**-1 infection which is of paramount importance for the initiation of effective therapeutic interventions. Since circulating maternal anti-**HIV**-1 antibody persists in the baby for up to 21 months, early conventional serological diagnosis of infection is not possible. Other methods for diagnosis of **HIV**-1 infection in a child less than 2 years of age have been utilized including the polymerase chain reaction (PCR), measurements of the **HIV**-1 p24 core protein and anti-**HIV**-1 **IgA**, as well in vitro measurements of antibody producing cells. In addition, the ability to predict **HIV**-1 infection in the child based upon maternal humoral immune responses to the **envelope** glycoprotein has also been suggested. This review summarizes the recent serological, biological and molecular methodologies used to predict and diagnose pediatric **HIV**-1 infection and AIDS.

L4 ANSWER 44 OF 99 MEDLINE on STN
95078000. PubMed ID: 7986587. Contrasting **IgA** and IgG neutralization capacities and responses to **HIV** type 1 **gp120** V3 loop in **HIV**-infected individuals. Kozlowski P A; Chen D; Eldridge J H; Jackson S. (Department of Microbiology, University of Alabama at Birmingham 35294.) AIDS research and human retroviruses, **(1994 Jul)** 10 (7) 813-22. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.
AB Quantitative analysis for **HIV**-1-specific antibodies present in **IgA** and IgG preparations purified from the serum of **HIV**-seropositive individuals indicated that the proportion of **HIV**-specific antibodies present within the IgG isotype was seven times greater than the proportion of **IgA HIV** antibodies present within the **IgA** isotype. Dilution of **IgA HIV**-specific antibodies by nonspecific **IgA** was observed in patients with elevated serum **IgA** concentrations, whereas proportions of IgG **HIV** antibodies rose with increases in concentrations of serum IgG. Although proportions of **IgA HIV** antibodies were not observed to correlate with the CD4 counts of the individuals from whom immunoglobulins were purified, a significant association between the numbers of such cells and proportion of **HIV** antibodies present in the IgG isotype was found. Equivalent amounts of IgG were also more effective than **IgA** at inhibiting **HIV**-1IIIB infection of a susceptible T cell line. This may be due to the presence of higher proportions of IgG antibodies directed toward non-V3 determinants because reactivity against an **HIV**-1IIIB V3 peptide was low and did not differ significantly between these isotopes. **IgA** antibodies reacting against a V3 peptide containing the **HIV** consensus sequence could be detected in the majority of **IgA** samples purified from infected individuals. Proportions of IgG consensus V3-specific antibodies within the purified IgG samples were, however, much higher. The presence of accompanying increases in serum IgG concentration and proportions of IgG **HIV** antibodies, higher proportions of both **HIV**- and consensus V3-specific antibodies within this isotype, and more effective neutralization by IgG suggests that an **HIV**-driven response is dominated by B cells committed to production of this immunoglobulin isotype. The observed low proportions of **HIV** antigen-specific **IgA** antibodies with dilution in many individuals by elevations in non-**HIV**-specific **IgA** suggests that **IgA** B cells may be more susceptible to factors that mediate the polyclonal activation believed to be responsible for many of the B cell disorders characteristic of **HIV** infection.

L4 ANSWER 45 OF 99 MEDLINE on STN
95074881. PubMed ID: 7983725. Synthetic multimeric peptides derived from the principal neutralization domain (V3 loop) of **human**

immunodeficiency virus type 1 (**HIV-1**) **gp120** bind to galactosylceramide and block **HIV**-1 infection in a human CD4-negative **mucosal** epithelial cell line. Yahi N; Sabatier J M; Baghdiguian S; Gonzalez-Scarano F; Fantini J. (CNRS URA 1455, Laboratoire de Biochimie, Faculte de Medecine Nord, Marseille, France.) Journal of virology, **(1995 Jan)** 69 (1) 320-5. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB The glycosphingolipid galactosylceramide (GalCer), which binds **gp120** with high affinity and specificity, is a potential alternative receptor for **human immunodeficiency virus** type 1 (**HIV**-1) in some CD4-negative neural and epithelial human cells, including the human colonic epithelial cell line HT-29. In the present study, we demonstrate that synthetic multibranched peptides derived from the consensus sequence of the **HIV**-1 V3 loop block **HIV**-1 infection in HT-29 cells. The most active peptide was an eight-branched multimer of the motif Gly-Pro-Gly-Arg-Ala-Phe which at a concentration of 1.8 microM induced a 50% inhibition of **HIV**-1 infection in competition experiments. This peptide was not toxic to HT-29 cells, and preincubation with **HIV**-1 did not affect viral infectivity, indicating that the antiviral activity was not due to a nonspecific virucidal effect. Using a high-performance thin-layer chromatography binding assay, we found that multibranched V3 peptides recognized GalCer and inhibited binding of recombinant **gp120** to the glycosphingolipid. In addition, these peptides abolished the binding of an anti-GalCer monoclonal antibody to GalCer on the surface of live HT-29 cells. These data provide additional evidence that the V3 loop is involved in the binding of **gp120** to the GalCer receptor and show that multibranched V3 peptides are potent inhibitors of the GalCer-dependent pathway of **HIV**-1 infection in CD4-negative **mucosal** epithelial cells.

L4 ANSWER 46 OF 99 MEDLINE on STN

95046928. PubMed ID: 7958470. Expression of **human immunodeficiency virus** antigens in an attenuated Salmonella typhi vector vaccine. Hone D M; Lewis G K; Beier M; Harris A; McDaniels T; Fouts T R. (Department of Geographic Medicine, School of Medicine, University of Maryland, Baltimore.) Developments in biological standardization, **(1994)** 82 159-62. Ref: 9. Journal code: 0427140. ISSN: 0301-5149. Pub. country: Switzerland. Language: English.

AB **Human immunodeficiency virus** is known to enter the host at parenteral and **mucosal** sites and consequently an effective vaccine should stimulate immunity at both routes of entry. One approach toward stimulating **HIV**-specific **mucosal** and systemic immunity is the use of candidate live oral Salmonella typhi vector vaccine, strain CVD 908, which has been shown to stimulate **mucosal** and systemic immunity in volunteers. Using recombinant DNA techniques we constructed an expression cassette which comprises the lpp promoter (Plpp) and sequences encoding recombinant **gp120** (rgp120). When the Plpp-rgp120 expression cassette is integrated into the chromosome of CVD 908 in the delta aroC allele, high levels of recombinant **gp120** expression are observed. It is likely that effective immunity against **HIV** in humans will require immunization with multiple **HIV** antigens. Hence, a second expression cassette encoding two additional **HIV** antigens with vaccine potential, p24 (a **HIV**-1 gag gene product) and Nef (a putative regulator of **HIV**-1 gene expression) has been constructed. We plan to integrate the p24-Nef-encoding expression cassette into the aroD locus in the chromosome of CVD 908 delta aroC::rgp120 in a stable manner to produce a CVD 908-**HIV** vector vaccine that expresses multiple **HIV** antigens.

L4 ANSWER 47 OF 99 MEDLINE on STN

94368445. PubMed ID: 8086136. Immune response following oral administration of cholera toxin B subunit to **HIV**-1-infected UK and Kenyan subjects. Lewis D J; Gilks C F; Ojoo S; Castello-Branco L R; Dougan G; Evans M R; McDermott S; Griffin G E. (Division of Communicable Diseases, St George's Hospital Medical School, London, UK.) AIDS (London, England), **(1994 Jun)** 8 (6) 779-85. Journal code: 8710219. ISSN: 0269-9370. Pub. country: United States. Language: English.

AB OBJECTIVE: To determine the effect of **HIV**-1 infection on immunoglobulin (Ig) G and **IgA** antibody response and circulating antibody forming cell response to oral immunization with the B subunit of cholera toxin. DESIGN: Healthy UK volunteers, and **HIV**-1-positive UK and Kenyan volunteers at different clinical stages of **HIV**-1 infection received two oral immunizations. CD4+ T cells, serum beta 2-microglobulin and neopterin were measured as surrogate markers of disease stage, and correlated with immunization response. METHODS: Serum antitoxin IgG and **IgA** measured by enzyme-linked immunosorbent assay and antitoxin IgG, **IgA** and IgM antibody-forming cells detected by enzyme-linked immunospot assay at different times after two oral immunizations. RESULTS: UK **HIV**-positive volunteers (mean CD4+ T cell count, 52 x 10(6)/l) responded poorly to primary and booster immunization. **HIV**-infected Kenyans (752 x 10(6)/l CD4+ T cells) had a significant primary and booster antibody

response, whereas those with a mean CD4+ T cell count 186 x 10(6)/l had an insignificant primary, but significant booster response. Two oral immunizations induced antibody responses in **HIV**-positive Kenyan groups (who may have prior immunity from exposure to **environmental** bacterial toxins) of similar or greater magnitude to healthy UK volunteers. CONCLUSIONS: **Mucosal** immunization may recall immune memory and be of benefit in early and moderately advanced clinical **HIV** disease. The findings have important clinical implications in that mucosally targeted vaccines are potentially useful in this group of patients.

L4 ANSWER 48 OF 99 MEDLINE on STN

94308593. PubMed ID: 8035014. Intestinal **mucosal** immunoglobulins during **human immunodeficiency virus** type 1 infection. Janoff E N; Jackson S; Wahl S M; Thomas K; Peterman J H; Smith P D. (Department of Medicine, VA Medical Center, Minneapolis, MN 55417.) Journal of infectious diseases, **(1994 Aug)** 170 (2) 299-307. Journal code: 0413675. ISSN: 0022-1899. Pub. country: United States. Language: English.

AB In intestinal fluid samples from 39 **human immunodeficiency virus** type 1 (**HIV**-1)-infected patients, **IgA** and IgG levels were equivalent, whereas in 10 controls, **IgA** levels were significantly higher than those of IgG ($P < .05$). Intestinal **IgA** in patients contained predominantly monomeric IgA1, whereas IgA1 and IgA2 subclass levels in controls were nearly equivalent and primarily polymeric. The predominance of IgG and monomeric IgA1 in **mucosal** fluid samples from **HIV**-1-infected patients suggests exudation of serum immunoglobulins into the intestine. The decreased proportion of **mucosal** plasma cells producing **IgA** and IgA2 in the **HIV**-1-infected patients ($P < .01$) may also contribute to the abnormal intestinal immunoglobulin levels. Intestinal IgG reacted with most **HIV**-1 antigens, whereas specific **IgA** was present in only 10 of 17 patients and reacted with only **envelope** (**gp120** and **gp160**) and, less often, core (p17 and p24) antigens. Aberrant **mucosal** antibody responses and decreased integrity of the **mucosal** barrier may contribute to the intestinal dysfunction and infections that characterize **HIV**-1 infection.

L4 ANSWER 49 OF 99 MEDLINE on STN

94304040. PubMed ID: 8030973. Inactivation of **enveloped** viruses in human bodily fluids by purified lipids. Isaacs C E; Kim K S; Thormar H. (Department of Developmental Biochemistry, New York State Institute for Basic Research in Developmental Disabilities, Staten Island 10314.) Annals of the New York Academy of Sciences, **(1994 Jun 6)** 724 457-64. Ref: 42. Journal code: 7506858. ISSN: 0077-8923. Pub. country: United States. Language: English.

AB Antimicrobial lipids are found in **mucosal** secretions and are one of a number of nonimmunologic and nonspecific protective factors found at **mucosal** surfaces. Lipids can inactivate **enveloped** viruses, bacteria, fungi, and protozoa. Lipid-dependent antimicrobial activity at **mucosal** surfaces is due to certain monoglycerides and fatty acids that are released from triglycerides by lipolytic activity. Medium chain length antiviral lipids can be added to human blood products that contain **HIV**-1 and **HIV**-2 and reduce the cell-free virus concentration by as much as 11 log10 TCID50/ml. The presence of lipids does not interfere with most clinical assays performed on human blood samples. Antimicrobial lipids can disrupt cell membranes and therefore lyse leukocytes which potentially carry virus. Genital **mucosal** epithelial cells should be protected from damage by the mucous layer. Preliminary studies indicate that lipids decrease sperm motility and viability suggesting that lipids may potentially be used as combination spermicidal and virucidal agents.

L4 ANSWER 50 OF 99 MEDLINE on STN

94210365. PubMed ID: 8158535. IgG, IgM, and **IgA** response to **HIV** in infants born to **HIV**-1 infected mothers. Swiss Neonatal **HIV** Study Group. Schupbach J; Tomasik Z; Jendis J; Boni J; Seger R; Kind C. (Swiss National Center for Retroviruses, University of Zurich.) Journal of acquired immune deficiency syndromes, **(1994 May)** 7 (5) 421-7. Journal code: 8812597. ISSN: 0894-9255. Pub. country: United States. Language: English.

AB Children born to **HIV**-1-positive mothers were prospectively tested for **HIV**-reactive IgG, IgM, and **IgA** by Western blot, in order to study the children's humoral immune response in the background of passively transferred maternal IgG. In infected infants, a response was first seen at 1-3 months for **env**-reactive IgM and **IgA**, as well as gag-reactive IgM and IgG. This was followed by production of IgG to **env**, **IgA** to pol and to gag p17 and p55 at 7-9 months, and IgG to pol at 10-12 months. IgG Western blot positivity by all interpretation guidelines in all infected infants was found by 10-12 months. Subsequently, only IgG to **env** and p24, and **IgA** to **env** were maintained in all, whereas IgG to pol and p17 disappeared again in a significant fraction. A considerable proportion of uninfected infants also produced gag-reactive antibodies: IgM at 1-3 months, followed by IgG, which persisted in 10-20% and were

also found in children born to uninfected mothers. These antibodies were, however, present at lower titers than in infected infants and were apparently produced in response to agent(s) different from **HIV**. Maternal antibodies to **env** disappeared significantly faster in infected than uninfected infants. Traces of **HIV**-reactive IgG were present for up to 21 months in children who subsequently seroreverted completely.

L4 ANSWER 51 OF 99 MEDLINE on STN

94209687. PubMed ID: 8157978. Serum **IgA**-mediated neutralization of **HIV** type 1. Burnett P R; VanCott T C; Polonis V R; Redfield R R; Birx D L. (U.S. Army Dental Research Detachment, Washington, DC 20307.) Journal of immunology (Baltimore, Md. : 1950), **(1994 May 1)** 152 (9) 4642-8. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB The sera of 33 **HIV**-1-infected individuals, previously shown to neutralize **HIV**-1MN in vitro, were screened by ELISA for **IgA** reactivity against rgp120MN and a synthetic V3MN loop peptide. Six were selected for evaluation of the effect of serum **IgA** from infected individuals on the in vitro infection of susceptible target cells by **HIV**-1MN. By using protein G immobilized on Sepharose, we depleted the sera of IgG to a level undetectable by nephelometry and viral **envelope**-specific ELISA. The **IgA** component of the IgG-depleted serum was affinity purified with immobilized jacalin, a lectin that selectively binds the IgA1 fraction of human Ig. IgG-depleted sera and purified IgA1 serum fractions showing **IgA** reactivity against rgp120MN and V3MN by ELISA inhibited the in vitro infection of CEM-ss cells by **HIV**-1MN, but sera depleted of both IgG and IgA1 did not. These data show that, like serum IgG, serum **IgA** from selected **HIV**-1-infected individuals is capable of neutralizing **HIV**-1MN in vitro. The biologic significance of this observation and the identities of serum **IgA**-recognized **HIV**-1 neutralization epitopes remain to be determined.

L4 ANSWER 52 OF 99 MEDLINE on STN

94196732. PubMed ID: 7908473. Isotypes and IgG subclasses of anti-Fab antibodies in **human immunodeficiency virus**-infected hemophilia patients. Susal C; Oberg H H; Daniel V; Dorr C; Terness P; Huth-Kuhne A; Zimmermann R; Opelz G. (Department of Transplantation Immunology, University of Heidelberg, FRG.) Vox sanguinis, **(1994)** 66 (1) 37-45. Journal code: 0413606. ISSN: 0042-9007. Pub. country: Switzerland. Language: English.

AB We reported recently that anti-Fab autoantibodies of the IgG isotype are associated with the decrease of helper/inducer (CD4+) lymphocytes in **human immunodeficiency virus**-infected (**HIV**+) hemophilia patients with acquired immunodeficiency syndrome (AIDS) or AIDS-related complex (ARC). In the present study we investigated the subclass distribution of IgG-anti-Fab autoantibodies, and whether anti-Fab antibodies of the **IgA** and IgM isotypes also are associated with the development of AIDS. Sera of **HIV**+ patients with AIDS had significantly higher **IgA**-anti-Fab activity than **HIV**+ patients with ARC ($p < 0.02$), **HIV**+ patients without AIDS/ARC ($p < 0.0001$), **HIV**-negative (**HIV**-) patients ($p < 0.001$), or healthy controls ($p < 0.0001$). An inverse association was found between **IgA**-anti-Fab activity and CD4+ cell counts ($r = -0.396$, $p < 10(-6)$). In contrast, no association of CD4+ cell counts was observed with IgM-anti-Fab. However, IgM-anti-Fab was significantly increased in patients with thrombocytopenia. We found a significant association between **IgA**-anti-Fab activity and serum neopterin concentrations ($r = 0.310$, $p < 10(-5)$). IgG-anti-Fab activity was detected mainly in the IgG3 fraction, although in **HIV**+ patients with AIDS/ARC various IgG subclasses were present. Affinity-purified anti-Fab antibodies isolated from sera of AIDS patients bound to rgp120-preincubated CD4+ cells of a healthy individual, supporting our hypothesis that anti-Fab antibodies and free circulating **gp120** molecules are involved in the elimination of uninfected CD4+ cells. Removal of anti-Fab autoantibodies from the circulation by immune adsorbance might be a useful approach in the treatment of AIDS.

L4 ANSWER 53 OF 99 MEDLINE on STN

94180312. PubMed ID: 8133447. Detection of rectal antibodies to **HIV**-1 by a sensitive chemiluminescent western blot immunodetection method. Mohamed O A; Ashley R; Goldstein A; McElrath J; Dalessio J; Corey L. (Department of Epidemiology, School of Public Health, University of Washington, Seattle.) Journal of acquired immune deficiency syndromes, **(1994 Apr)** 7 (4) 375-80. Journal code: 8812597. ISSN: 0894-9255. Pub. country: United States. Language: English.

AB Western blot with a time-dependent enhanced chemiluminescence immunodetection method (ECL-WB) was shown to be 100-fold more sensitive than standard commercial colorimetric Western blots (WB) for detecting serum IgG to **human immunodeficiency virus** type 1 (**HIV**-1). ECL-WB was then used to test rectal secretions from 15 **HIV**-1 infected subjects

(**HIV+**) and 7 uninfected subjects (**HIV-**) to document local IgG, **IgA**, and secretory component-associated immunoglobulin (SC-Ig) to **HIV**-1 proteins. Fourteen of 15 **HIV+** subjects had rectal **IgA** to at least 1 **HIV**-1 protein, most often to **gp41** (80%) or p24 (60%) and 14 (93%) had IgG to **gp160**, **gp120**, or **gp41**. Of seven **HIV-** subjects, none had detectable bands to **HIV**-1 proteins. SC-Ig to **HIV**-1 proteins was detected in all five rectal samples tested. However, the antibody profiles differed from those of rectal **IgA**, suggesting more than one source of rectal **IgA** to **HIV**. ECL-WB requires individual optimization and interpretation for each specimen as well as expensive reagents and is, therefore, not currently applicable to screening assays. However, the method offers promise as a sensitive method to characterize low-level immune responses (IgG, **IgA**, and SC-Ig) to **HIV**-1 proteins at local sites such as rectal mucosae.

L4 ANSWER 54 OF 99 MEDLINE on STN

94133801. PubMed ID: 7905554. Maternal IgG1 and **IgA** antibody to V3 loop consensus sequence and maternal-infant **HIV**-1 transmission. Markham R B; Coberly J; Ruff A J; Hoover D; Gomez J; Holt E; Desormeaux J; Boulos R; Quinn T C; Halsey N A. (Department of Immunology and Infectious Diseases, Johns Hopkins University School of Hygiene and Public Health, Baltimore, MD 21205.) Lancet, **(1994 Feb 12)** 343 (8894) 390-1. Journal code: 2985213R. ISSN: 0140-6736.
Report No.: PIP-093464; POP-00229627. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Maternal-infant transmission of **HIV**-1 occurs in 13-40% of pregnancies. Studies on transmission of maternal immunity to **HIV** antigens have used antigens from viruses not representative of clinical isolates and have been conflicting. Using a consensus peptide sequence based on **HIV** isolates found in Haiti, we found that Haitian mothers who transmitted infection to their offspring had significantly higher mean concentrations of IgG1 antibodies to the V3 loop of the primary neutralising domain of the viral **envelope** (gp 160) than non-transmitters ($p = 0.02$). Concentrations of **IgA** antibody to this domain were similar in transmitters and non-transmitters.

L4 ANSWER 55 OF 99 MEDLINE on STN

94127077. PubMed ID: 8296480. Oral immunization with recombinant BCG induces cellular and humoral immune responses against the foreign antigen. Lagranderie M; Murray A; Gicquel B; Leclerc C; Gheorghiu M. (Laboratoire du BCG, Institut Pasteur de Paris, France.) Vaccine, **(1993 Oct)** 11 (13) 1283-90. Journal code: 8406899. ISSN: 0264-410X. Pub. country: ENGLAND: United Kingdom. Language: English.

AB It has been shown recently that BCG can be used as a live recombinant vaccine to stimulate immune responses. Proliferative or cytotoxic T-cell responses against several viral proteins such as **HIV** Gag, **Env** or Nef were obtained after parenteral immunization with BCG expressing these proteins. Antibody responses were also obtained after immunization of mice with recombinant BCG strain which expressed lac Z under the control of a promoter sequence isolated from Mycobacterium paratuberculosis. We have used this recombinant vaccine in guinea-pigs to investigate the influence of various routes of immunization on the immunogenicity of a foreign antigen expressed by recombinant BCG. Guinea-pigs were immunized by oral, respiratory or intradermal routes and proliferative responses, delayed-type hypersensitivity and antibody responses specific for beta-galactosidase were followed for 16 weeks. Results demonstrated that humoral and cellular immune responses specific for beta-galactosidase can be produced in all groups of guinea-pigs. However, the respiratory and especially the oral route of administration induced higher local and systemic immune responses than the intradermal route of immunization. Moreover, the oral immunization of mice with this recombinant BCG induced **IgA** responses which could be detected in both sera and intestinal secretions. Therefore, this study demonstrates for the first time that oral immunization with recombinant BCG can induce strong cellular and humoral immune responses.

L4 ANSWER 56 OF 99 MEDLINE on STN

94053541. PubMed ID: 8235446. Characteristics of **IgA** antibodies against **HIV**-1 in sera and saliva from **HIV**-seropositive individuals in different clinical stages. Matsuda S; Oka S; Honda M; Takebe Y; Takemori T. (AIDS Research Center, National Institute of Health, Tokyo, Japan.) Scandinavian journal of immunology, **(1993 Nov)** 38 (5) 428-34. Journal code: 0323767. ISSN: 0300-9475. Pub. country: ENGLAND: United Kingdom. Language: English.

AB **IgA** antibodies were analysed in sera and saliva from 40 **HIV**-1 seropositive individuals. The level of total **IgA** in serum was elevated according to the progress of the disease. **IgA** antibodies against p24 and **gp160** were detected in the asymptomatic phase of infection. However, they declined in the symptomatic phases in contrast with IgG

antibodies. Interestingly, three patients in the symptomatic phase who showed high levels of **IgA** antibodies were all in relatively good clinical condition. The IgG and **IgA** antibodies in saliva declined in the symptomatic phase. The level of IgG anti-p24 antibodies in saliva correlated with that in serum, suggesting that IgG anti-p24 antibodies in saliva originated from those in the serum. These results indicate that **IgA** antibodies are regulated independently from IgG antibodies and that the **mucosal** immune system is impaired early in the symptomatic phase of **HIV** infection, which starts with **mucosal** impairment. Detection of **IgA** antibodies may be useful for prognosis of the disease in **HIV**-infected individuals. The results indicate also that treatment for the impaired **IgA mucosal** immune system should be taken into consideration.

L4 ANSWER 57 OF 99 MEDLINE on STN

93378784. PubMed ID: 8369168. Antibodies to recombinant **gp160** in **mucosal** secretions and sera of persons infected with **HIV**-1 and seronegative vaccine recipients. Funkhouser A; Clements M L; Slome S; Clayman B; Viscidi R. (Center for Immunization Research, Johns Hopkins University School of Hygiene and Public Health, Baltimore, Maryland 21205.) AIDS research and human retroviruses, **(1993 Jul)** 9 (7) 627-32. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.

AB An enzyme immunoassay (EIA) was developed to detect secretory **IgA** (sIgA) antibodies to **HIV**-1 **envelope** glycoprotein, using a mouse monoclonal antibody and a highly purified, baculovirus-expressed recombinant **gp160** (rgp160) as antigen. Detection of sIgA was enhanced by prior immunoprecipitation of IgG. IgG and sIgA rgp160 antibodies were measured in parotid saliva and nasal wash samples of 18 **HIV**-1-seropositive volunteers and 14 **HIV**-1-seronegative adult volunteers immunized 3 times with **HIV**-1 IIIB rgp160 vaccine at 1 of 4 dosage levels: 40 micrograms (N = 3), 80 micrograms (N = 3), 160 micrograms (N = 4), and 640 micrograms (N = 4). We detected rgp160-specific IgG antibody in the nasal wash samples of all **HIV**-1-seropositive volunteers and 4/8 vaccinees (50%) immunized with the two highest doses of rgp160 vaccine. All infected volunteers tested had rgp160-specific sIgA in their nasal wash samples. None of the vaccinees and very few of infected volunteer specimens had detectable antibody in the parotid saliva samples (5/8 had IgG and 1/8 had sIgA). We also detected IgG antibody to rgp160 in the sera of all infected volunteers and 13/14 vaccinees (93%). With this EIA, sIgA antibody can be measured in **mucosal** secretions of recipients of appropriate candidate **HIV**-1 vaccines.

L4 ANSWER 58 OF 99 MEDLINE on STN

93327796. PubMed ID: 8335015. Early detection of **IgA** specific antibodies in **HIV**-1 infected children by peptide-ELISA and peptide time-resolved fluoro-immunoassay. Lombardi V; Caniglia M; Scarlatti G; Jansson M; Plebani A; D'Argenio P; Scaccia S; Wigzell H; Rossi P. (Department of Immunology, Karolinska Institute, Stockholm, Sweden.) European journal of pediatrics, **(1993 Jun)** 152 (6) 484-9. Journal code: 7603873. ISSN: 0340-6199. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB The presence of specific **IgA** antibodies in sera from 25 infants born to **HIV**-1 seropositive mothers was investigated by peptide-ELISA and peptide time-resolved fluoro-immunoassay (TR-FIA). The infants had been monitored at different times after birth for clinical signs and/or symptoms of **HIV**-1 infection and for detection of **HIV**-1 in lymphocyte cultures. Serum samples had also been tested for **HIV**-1 IgG antibodies by commercial ELISA and Western blot and for p24 antigen. Eleven of 25 children were then identified as infected. **IgA** detection was performed after rProtein G treatment to remove interfering IgG. In the infected group, **IgA** specific antibodies to a synthetic peptide representing a highly conserved region of the transmembrane glycoprotein **gp41** (**env**: 594-613) were detected in 27 (73%) out of 37 serum samples (9 of 11 children) by the peptide-ELISA test. **IgA** specific antibodies to the same peptide were found in 30 (81%) sera (9 of 11 children) by the peptide-TR-FIA. Specific **HIV**-1 **IgA** antibodies were detected as early as 2 months of age in serum samples from five out of seven children (71% sensitivity) using peptide-ELISA and from six out of seven (86% sensitivity) by peptide-TR-FIA. Conversely, **IgA** specific antibodies to **HIV**-1 were absent in two infected children as well as in the sera of all uninfected children tested during the follow up period. Since maternal **IgA** does not cross the placenta, **IgA** detection in the serum of the infant is indicative of **HIV**-1 infection.(ABSTRACT TRUNCATED AT 250 WORDS)

L4 ANSWER 59 OF 99 MEDLINE on STN

93295180. PubMed ID: 8100017. Antibody to specific **HIV**-1 proteins in oral **mucosal** transudates. Cheingsong-Popov R; Callow D; Weber J; Holm-Hansen C; Constantine N T. Lancet, **(1993 Jun 26)** 341 (8861) 1659-60. Journal code: 2985213R. ISSN: 0140-6736. Pub. country: ENGLAND:

United Kingdom. Language: English.

L4 ANSWER 60 OF 99 MEDLINE on STN
93292188. PubMed ID: 8099858. Loss of **mucosal** CD4 lymphocytes is an early feature of **HIV** infection. Lim S G; Condez A; Lee C A; Johnson M A; Elia C; Poulter L W. (Department of Medicine, Royal Free Hospital, School of Medicine, London, UK.) Clinical and experimental immunology, **(1993 Jun)** 92 (3) 448-54. Journal code: 0057202. ISSN: 0009-9104. Pub. country: ENGLAND: United Kingdom. Language: English.
AB T cell subsets in the gut mucosa are distinct populations and their imbalance in **HIV** has specific implications in infection. Alterations in T cell subsets in duodenal biopsies were investigated in 17 asymptomatic **HIV** patients, 24 AIDS patients and 10 controls with non-ulcer dyspepsia. Immunohistochemistry and immunofluorescence using MoAbs to CD3, CD4, CD8, CD68, CD45RA, CD45RO and **gp120** were performed on frozen sections. In the lamina propria, there was a significant depletion of CD4+ cells at all stages of **HIV**, but the density of CD8 lamina propria cells was increased. Intraepithelial lymphocytes were decreased in AIDS patients. There was a significant correlation between cellular density and **mucosal** CD3+ lymphocytes, and between **mucosal** CD3+ and CD8+ lymphocytes. Although **mucosal** CD4,CD45RO+ 'memory' cells were decreased, CD8,CD45RO+ 'memory' cells were increased. **Mucosal** CD4+ lymphocyte depletion occurred early in **HIV**, and thus their role in **mucosal** protection against opportunistic infection should be revised. **Mucosal** CD8+ lymphocytes initially increased, but decreased when CD4 blood counts were depleted, perhaps contributing to loss of host protection against infection. Intraepithelial lymphocyte depletion may also contribute to opportunistic infection.

L4 ANSWER 61 OF 99 MEDLINE on STN
93292187. PubMed ID: 8513576. **Mucosal** macrophage subsets of the gut in **HIV**: decrease in antigen-presenting cell phenotype. Lim S G; Condez A; Poulter L W. (University Department of Medicine, Royal Free Hospital School of Medicine, London, UK.) Clinical and experimental immunology, **(1993 Jun)** 92 (3) 442-7. Journal code: 0057202. ISSN: 0009-9104. Pub. country: ENGLAND: United Kingdom. Language: English.
AB The effect of **HIV** infection on intestinal lamina propria macrophage subsets was investigated in 41 patients at various stages of **HIV** infection (asymptomatic **HIV** infection, n = 17; AIDS, n = 24). Duodenal biopsies taken from **HIV** patients at endoscopy were snap frozen and cryostat sections cut for immunohistochemical staining. MoAbs CD68 (EBM11, pan-macrophage marker), RFD1 (antigen-presenting cells) and RFD7 (mature phagocytic macrophages) were used to identify cell subsets using indirect immunoperoxidase or alkaline phosphatase. Double immunofluorescence using MoAbs to **HIV** proteins (p24, p17 and **gp120**) and RFD1 were used to identify **HIV**-infected antigen-presenting cells. Double immunofluorescence was also used to identify macrophages that expressed both RFD1 and RFD7 ('suppressor' macrophages). Intensity of HLA-DR expression in lamina propria cells was investigated using a MoAb to HLA-DR directly conjugated to glucose oxidase. The results show that there was no difference in overall density of macrophages, but there was a significant decrease in dendritic cells (RFD1+) in all clinical stages of **HIV**. There was no difference in the density of RFD7+ macrophages, nor was there a difference intensity of HLA-DR expression in lamina propria cells. Only four **HIV**-infected cells were positively identified in the 41 patients. This result suggests that the antigen-presenting arm of **mucosal** immune defences may be seriously compromised in **HIV** infection, and represents a further insult to **mucosal** immunity already impaired as a result of loss of CD4+ T lymphocytes. This may contribute to development of opportunist infection in the gut.

L4 ANSWER 62 OF 99 MEDLINE on STN
93253304. PubMed ID: 8486953. Anti-**gp160** IgG and **IgA** antibodies associated with a large increase in total IgG in cervicovaginal secretions from **human immunodeficiency virus** type 1-infected women. Lu X S; Belec L; Pillot J. (Unite d'Immunologie Microbienne, Institut Pasteur, Paris, France.) Journal of infectious diseases, **(1993 May)** 167 (5) 1189-92. Journal code: 0413675. ISSN: 0022-1899. Pub. country: United States. Language: English.
AB To study the specific local immune response in vaginal fluids, 19 women infected with **human immunodeficiency virus** (**HIV**) type 1 and 23 seronegative controls were selected. Vaginal fluids were tested by ELISA for total IgG, **IgA**, and IgM levels and for specific IgG, **IgA**, and IgM antibodies to **gp160**. Total IgG, **IgA**, and IgM concentrations were 6.8-, 5.0-, and 2.5-fold higher, respectively, in **HIV**-1-infected women than in controls, with a positive correlation between IgG and **IgA** levels. IgG or **IgA** antibodies or both to **gp160** were detected in 12 subjects (63%), whereas no IgM antibodies to **gp160** were found. Anti-**gp160** IgG strongly predominated. Serum samples were available for

11 women whose total IgG vaginal levels strongly correlated with total IgG in sera. These results suggest that transudation of serumborne antibodies is the main source of **gp160**-specific antibodies in the vaginal fluid of **HIV**-1-infected women.

L4 ANSWER 63 OF 99 MEDLINE on STN

93211206. PubMed ID: 8096270. Breast milk and **HIV**-1 transmission. Mok J. (Regional Infectious Diseases Unit, City Hospital, Edinburgh, UK.) Lancet, **(1993 Apr 10)** 341 (8850) 930-1. Journal code: 2985213R. ISSN: 0140-6736.
Report No.: PIP-081605; POP-00221161. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Leukocyte numbers, lactoferrin and **IgA** levels, and lymphocyte mitogenic activity in breast milk fall greatly to almost 0 during the first 2-3 months postpartum, but lactoferrin and **IgA** levels rise during the 3rd-12th month postpartum. Regardless of mother's **HIV**-1 status, breast-fed infants suffer fewer episodes of gastrointestinal and respiratory illnesses than do bottle-fed infants. Breast-fed, **HIV**-1 infected infants experience a longer median incubation period than do bottle-fed infants (19 vs. 9.7 months). The progression to AIDS in breast-fed infants is slower than in bottle-fed infants. The risk of **HIV**-1 transmission from a mother infected after delivery is 29% while it is 14% from a mother infected before delivery, suggesting that antibodies acquired transplacentally or through breast milk protect against **HIV**-1 infection in infants. Breast milk samples from 15 **HIV**-1 infected mothers reveal IgG and **IgA** antibodies against **envelope** glycoproteins and **IgA** antibodies against core antigens. A human milk factor blocks binding of **HIV**-1 to the CD4 receptor. A report in this issue of The Lancet shows **HIV**-1 specific IgM and **IgA** in 15-day postpartum breast milk, regardless of mother's immune status. There is a linear relationship between the persistence of these antibodies and the absence of **HIV**-1 infection in the infants. The authors believe neutralizing or cytotoxic activity protects infants against **HIV**-1 infection. More needs to be learned about **mucosal** transmission. If a cell-associated virus is responsible for **HIV**-1 infection, then the colostrum would be more infectious. Perhaps **HIV**-1 transmission could be reduced if mothers express and discard the colostrum and the early milk. This would be important to know, especially for women in developing countries. Further research is needed to learn how and when perinatal **HIV**-1 transmission occurs. In the interim, in areas where a safe alternative to breast milk exists, **HIV**-1 infected mothers should not breast feed.

L4 ANSWER 64 OF 99 MEDLINE on STN

93211200. PubMed ID: 8096264. Infective and anti-infective properties of breastmilk from **HIV**-1-infected women. Van de Perre P; Simonon A; Hitimana D G; Dabis F; Msellati P; Mukamabano B; Butera J B; Van Goethem C; Karita E; Lepage P. (National AIDS Control Programme, AIDS Reference Laboratory, Kigali, Rwanda.) Lancet, **(1993 Apr 10)** 341 (8850) 914-8. Journal code: 2985213R. ISSN: 0140-6736.
Report No.: PIP-081674; POP-00222812. Pub. country: ENGLAND: United Kingdom. Language: English.

AB **Human immunodeficiency virus** type 1 (**HIV**-1) is transmitted mainly by cell-to-cell contact. We postulated that transmission of **HIV**-1 through breastmilk could be favoured by the presence of infected cells, by deficiency of anti-infective substances in breastmilk, or both factors. 215 **HIV**-1-infected women were enrolled at delivery in Kigali, Rwanda; milk samples were collected 15 days, 6 months, and 18 months post partum. **HIV**-1 IgG, secretory **IgA**, and IgM were assayed by western blot, for the latter two after removal of IgG with protein G. In the 15-day and 6-month samples, we sought viral genome in milk cells by a double polymerase chain reaction with three sets of primers (gag, pol, and **env**). **HIV**-1 infection in the offspring was defined according to serological and clinical criteria. At 15 days, 6 months, and 18 months post partum, **HIV**-1 specific IgG was detected in 95%, 98%, and 97% of breastmilk samples, **IgA** in 23%, 28%, and 41%, and IgM in 66%, 78%, and 41%. In children who survived longer than 18 months, the probability of infection was associated with lack of persistence of IgM and **IgA** in their mothers' milk (adjusted chi 2 for trend, $p = 0.01$ for IgM and $p = 0.05$ for **IgA**). The presence of **HIV**-1-infected cells in the milk 15 days post partum was strongly predictive of **HIV**-1 infection in the child, by both univariate ($p < 0.05$) and multivariate analysis ($p = 0.01$). The combination of **HIV**-1-infected cells in breastmilk and a defective IgM response was the strongest predictor of infection. **HIV**-1 infection in breastfed children born to infected mothers is associated with the presence of integrated viral DNA in the mothers' milk cells. IgM and **IgA** anti-**HIV**-1 in breastmilk may protect against postnatal transmission of the virus.

L4 ANSWER 65 OF 99 MEDLINE on STN

93163242. PubMed ID: 1287035. Serum antibodies to **HIV**-1 in recombinant vaccinia virus recipients boosted with purified recombinant **gp160**. NIAID AIDS Vaccine Clinical Trials Network. Montefiori D C; Graham B S; Kliks S; Wright P F. (Department of Pathology, Vanderbilt University Medical School, Nashville, Tennessee 37232.) Journal of clinical immunology, **(1992 Nov)** 12 (6) 429-39. Journal code: 8102137. ISSN: 0271-9142. Pub. country: United States. Language: English.

AB Serum antibody responses were studied in detail in four vaccinia-naive volunteers in a phase I trial evaluating primary vaccination with a recombinant vaccinia virus expressing the **HIV**-1 **gp160 envelope** glycoprotein (HIVAC-1e, Oncogen/Bristol-Myers Squibb), followed by booster immunization with baculovirus-derived rgp160 (VaxSyn, MicroGeneSys). Prior to boosting, low-titer Fc receptor (FcR)-mediated, antibody-dependent enhancing (ADE) activity was detected in two of four volunteers but no IgM, IgG, **IgA**, neutralizing activity, or complement-mediated ADE activity was detected. Two weeks after boosting, all four volunteers developed **HIV**-1-specific IgG with titers of 1:160 to 1:640 by immunofluorescence assay. IgG1 was present in sera from each individual, while IgG2 and IgG3 were present in sera from two individuals, and IgG4 was present in serum from one individual. IgM and **IgA** were undetectable in all sera. Only one volunteer had IgG to the heterologous **HIV**-1 isolates, RF, MN, and SF2, after boosting. Serum from this volunteer neutralized the vaccine strain, LAV/IIIB, but not the heterologous strains, RF, MN, and SF2. Antibodies from the remaining volunteers had no neutralizing activity. The neutralizing serum had a positive reaction in a peptide-based ELISA utilizing a peptide corresponding to the principal neutralizing domain of the third hypervariable region (i.e., V3 loop) of the **envelope** glycoprotein. Neutralizing activity was partially removed by adsorption to this peptide, suggesting that it contained a type-specific neutralizing vaccine epitope. A low titer (1:40 to 1:80) of complement-mediated ADE activity to **HIV**-1 IIIB was present in sera from three vaccinees after boosting. FcR-ADE activity for **HIV**-1 SF2 and SF-128A were present in sera from two of these three vaccinees. None of the volunteers developed antisyncytial antibodies. These results indicate that inoculation with recombinant vaccinia followed by rgp160 boosting is the most effective strategy to date for inducing serum antibodies to the **envelope** glycoproteins of **HIV**-1, but further study is needed to optimize the functionality and cross-reactivity of these responses.

L4 ANSWER 66 OF 99 MEDLINE on STN

93139196. PubMed ID: 8423204. HTLV-1 antibody class and subclass distribution in African TSP and control populations. Verdier M; Bonis J; Leonard G; Dumas M; Denis F. (Laboratoire de Bacteriologie-Virologie, CHU Dupuytren, Limoges, France.) Journal of neuroimmunology, **(1993 Jan)** 42 (1) 117-20. Journal code: 8109498. ISSN: 0165-5728. Pub. country: Netherlands. Language: English.

AB The humoral immune responses in 44 sera from HTLV-1 seropositive African subjects were compared. The sample population was composed of 12 patients with HTLV-1 associated myelopathy/tropical spastic paraparesis (HAM/TSP), 12 patients with other neurological conditions and 20 asymptomatic carriers. Samples HTLV-1 antigens were tested against all immunoglobulin classes and IgG subclasses, using the Western blot technique with polyclonal and monoclonal antibodies. Whilst IgG reacted with gag, **env** and tax products for the three groups studied, IgM and **IgA** were found to react more frequently with HTLV-1 in HAM/TSP patients. For these patients, IgM and **IgA** were particularly directed against tax and **env** proteins. Among IgG subclasses, IgG1 was most sensitive to gag, **env** and tax products reacting in similar proportions in all three groups. IgG2 and IgG4 were apparently not involved. IgG3 was most responsive in HAM/TSP patients. These data are similar to those observed in AIDS patients, LAS and **HIV** asymptomatic carriers and emphasize the role of HTLV-1 in HAM/TSP.

L4 ANSWER 67 OF 99 MEDLINE on STN

93103816. PubMed ID: 1466960. Oral priming followed by parenteral immunization with **HIV**-immunosomes induce **HIV**-1-specific salivary and circulatory **IgA** in mice and rabbits. Thibodeau L; Tremblay C; Lachapelle L. (AIDS Laboratory, Institut Armand Frappier, University of Quebec, Laval, Canada.) AIDS research and human retroviruses, **(1992 Aug)** 8 (8) 1379. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.

L4 ANSWER 68 OF 99 MEDLINE on STN

93090459. PubMed ID: 1457191. Serum **IgA** subclasses and molecular forms in **HIV** infection: selective increases in monomer and apparent restriction of the antibody response to IgA1 antibodies mainly directed at **env** glycoproteins. Kozlowski P A; Jackson S. (Department of Microbiology, University of Alabama, Birmingham 35294.) AIDS research and

human retroviruses, **(1992 Oct)** 8 (10) 1773-80. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.

AB In a study population representing different CDC stages of **HIV** infection, 58% exhibited **IgA** hypergammaglobulinemia resulting from proportional increases in both the IgA1 and the IgA2 subclasses. These increases were detected early in infection, did not correlate with CD4 count, and remained elevated throughout disease progression. Absolute concentrations of polymeric **IgA** present within each subclass were unchanged, indicating that increased production of monomeric IgA1 and IgA2 were responsible for elevations of total **IgA**. These elevations were not completely attributable to a specific antibody response to viral infection, since Western blot analysis of purified **IgA** samples indicated that **HIV**-reactive **IgA** antibodies could be demonstrated only within the IgA1 subclass. Dominating IgA1 anti-**HIV** responses were also observed in two secretory **IgA** samples isolated from colostrum of healthy **HIV** seropositive mothers, suggesting that a similar isotype restriction exists in the **mucosal IgA** compartment. The binding of IgA1 to **HIV** proteins contrasted markedly to that observed with identical concentrations of IgG purified from the sera of the same patients. While IgG reacted more intensely and broadly with all **HIV** proteins, IgA1 antibodies were directed predominantly against **envelope** glycoproteins. In many patients, a total lack of IgA1 reactivity to gag and pol proteins was accompanied by intact IgG responses to these same antigens. Though all **IgA** samples examined reacted with **HIV**, fewer responses to **gp160**, **gp120**, and p24 were observed in samples from AIDS and AIDS-related complex (ARC) patients, suggesting a declining titer of **IgA** antibodies against these antigens may be associated with disease progression.(ABSTRACT TRUNCATED AT 250 WORDS)

L4 ANSWER 69 OF 99 MEDLINE on STN

93089780. PubMed ID: 1456648. M cell-mediated antigen transport and monoclonal **IgA** antibodies for **mucosal** immune protection. Amerongen H M; Weltzin R; Mack J A; Winner L S 3rd; Michetti P; Apter F M; Kraehenbuhl J P; Neutra M R. (Department of Pediatrics, Harvard Medical School, Boston, Massachusetts.) Annals of the New York Academy of Sciences, **(1992)** 664 18-26. Ref: 33. Journal code: 7506858. ISSN: 0077-8923. Pub. country: United States. Language: English.

L4 ANSWER 70 OF 99 MEDLINE on STN

93056681. PubMed ID: 1431241. Infection of accessory dendritic cells by **human immunodeficiency virus** type 1. Langhoff E; Haseltine W A. (Division of Human Retrovirology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA 02115.) Journal of investigative dermatology, **(1992 Nov)** 99 (5) 89S-94S. Ref: 75. Journal code: 0426720. ISSN: 0022-202X. Pub. country: United States. Language: English.

AB Many details of the pathogenesis of the **human immunodeficiency virus** type 1 remain to be elucidated. Details of how the virus gains entry via the **mucosal** surface upon sexual contact or during breast feeding remain obscure. The means by which the infection travels throughout the body as well as the nature of the major reservoirs of virus infection remains, for the most part, unknown. Recent studies raise the possibility that cells of the Langerhans/dendritic lineage play a central role in **human immunodeficiency virus** (**HIV**-1) infection and pathogenesis. It has been known for several years that veiled dendritic cells in the circulation as well as skin Langerhans are infected in people with prolonged **HIV**-1 infections. More recently it has been found that a large burden of viral DNA sequences is found, not only in the circulating T-cell population, but also in a population that is defined as a non-T, non-B, non-monocyte/macrophage population rich in T-helper dendritic cells. Detailed analysis of infection of primary blood-derived T-helper dendritic cells by **HIV**-1 shows that such cells are the most susceptible cells in the blood to infection by this virus. The cells also produce much more virus per cell than do purified populations of other blood mononuclear cells. Moreover, primary blood-derived T-helper dendritic cells are not killed by infection by **HIV**-1. These cells are susceptible to lymphotropic, monocyte tropic, and primary isolates of **HIV**-1. The sensitivity of primary blood-derived T-helper dendritic cells to infection by **HIV**-1 has been shown to be attributable to rapid uptake of virus particles as well as rapid synthesis of viral DNA. Subsequent steps of virus replication also occur more rapidly and more efficiently in populations of primary blood-derived T-helper dendritic cells than they do in purified preparations of blood-derived T cells and monocyte/macrophages. Studies with primates using the simian immunodeficiency virus (SIV) show that dendritic cells at the surface of sexual mucosa are rapidly infected upon exposure to high concentrations of the virus. SIV is also produced in abundance in Langerhans cells located at the surface of the sexual mucosa in animals infected for prolonged periods of time.

L4 ANSWER 71 OF 99 MEDLINE on STN
92357092. PubMed ID: 1495523. Brief report: idiotypic **IgA** nephropathy in patients with **human immunodeficiency virus** infection. Kimmel P L; Phillips T M; Ferreira-Centeno A; Farkas-Szallasi T; Abraham A A; Garrett C T. (Department of Medicine, George Washington University Medical Center, Washington, D.C. 20037.) New England journal of medicine, **(1992 Sep 3)** 327 (10) 702-6. Journal code: 0255562. ISSN: 0028-4793. Pub. country: United States. Language: English.

L4 ANSWER 72 OF 99 MEDLINE on STN
92356096. PubMed ID: 1645152. Vaginal immunization of rats with a synthetic peptide from **human immunodeficiency virus envelope** glycoprotein. O'Hagan D T; Rafferty D; McKeating J A; Illum L. (Department of Pharmaceutical Sciences, University of Nottingham, University Park, U.K.) Journal of general virology, **(1992 Aug)** 73 (Pt 8) 2141-5. Journal code: 0077340. ISSN: 0022-1317. Pub. country: ENGLAND: United Kingdom. Language: English.
AB Local secretory immunity in the vagina may confer a degree of protection against heterosexual transmission of **human immunodeficiency virus (HIV)**. Since the vagina has been shown to respond to local immunization, we have undertaken intravaginal immunization of rats with a 20-mer peptide (amino acid residues 102 to 121) of the **HIV-1 envelope** glycoprotein (**gp120**). The peptide was administered in combination with an 'absorption enhancer', lysophosphatidyl glycerol (LPG), which has previously been shown to promote the absorption of intravaginally administered peptides, while exerting only mild effects on epithelial membrane integrity. Intravaginal immunization with LPG and the peptide induced serum and vaginal wash **IgA** and IgG antibody responses which were enhanced in comparison to those after immunization with the peptide alone. Serum antibodies induced by both subcutaneous and intravaginal immunization were able to recognize recombinant **HIV-1 gp120**. However, the rat antiserum displayed no neutralizing activity against the virus. These results demonstrate that LPG is an effective immunological adjuvant for intravaginally administered peptide antigens. An alternative absorption enhancer, bestatin (BES), was not effective as an immunological adjuvant when administered intravaginally and blocked the adjuvant activity of LPG when BES and LPG were used in combination.

L4 ANSWER 73 OF 99 MEDLINE on STN
92224934. PubMed ID: 1563380. Immunoblotting analysis of **IgA** and IgM antibody to **human immunodeficiency virus** type 1 (**HIV**-1) polypeptides in seropositive infants. Re M C; Furlini G; Vignoli M; Zauli G; Dallacasa P; Masi M; La Placa M. (Institute of Microbiology, University of Bologna, St. Orsola Hospital, Italy.) European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology, **(1992 Jan)** 11 (1) 27-32. Journal code: 8804297. ISSN: 0934-9723. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.
AB Seventy infants born to **human immunodeficiency virus** type 1 (**HIV**-1) seropositive mothers were studied for specific antibody (**IgA**, IgM and IgG) production and the presence of active infection (detectable level of virus in peripheral blood lymphocytes). Among these children, followed for up to 15-40 months after birth, 11 presented unequivocal signs of **HIV**-1 infection (persistent p24 antigenemia and/or positive virus isolation). Analysis of sera by immunoblotting showed that **IgA** antibody to **HIV**-1 p24 core protein, alone or associated with **envelope** glycoproteins (**gp120, gp41**), was present in the majority of infected babies (7 of 11), while IgM was found in a lower percentage of cases (4 of 11). No **IgA** and or IgM antibody to **HIV**-1 was ever found in babies, born to seropositive mothers, who seroreverted after birth or in the control group enrolled in this study. Our results indicate that immunoblotting analysis of **IgA** antibody to **HIV**-1 polypeptides may represent a useful complementary prognostic marker in children born to **HIV**-1 seropositive mothers.

L4 ANSWER 74 OF 99 MEDLINE on STN
92148648. PubMed ID: 1738088. A comparison of **HIV**-1 antibody classes, titers, and specificities in paired semen and blood samples from **HIV**-1 seropositive men. Wolff H; Mayer K; Seage G; Politch J; Horsburgh C R; Anderson D. (Department of Obstetrics, Gynecology, and Reproductive Biology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts 02115.) Journal of acquired immune deficiency syndromes, **(1992)** 5 (1) 65-9. Journal code: 8812597. ISSN: 0894-9255. Pub. country: United States. Language: English.
AB Twenty-eight paired blood and semen samples obtained from **human immunodeficiency virus** type 1 (**HIV**-1) seropositive men at various stages of disease progression were evaluated for titer and immunoglobulin (Ig) class by an enzyme-linked immunosorbent assay (ELISA). Blood antibody titers ranged from 40,000 to 4,000,000 with a median of 40,000.

Semen titers ranged from 400 to 40,000 with a median of 400. **HIV**-1 antibody titers in matched semen and blood samples showed a strong positive correlation (r = 0.963). The ratio of semen:blood titers ranged from 1:1000 to 1:10 with a median of 1:100. There was no correlation between blood or semen antibody titer and stage of disease of the patients. However, there was a trend toward higher (greater than or equal to 4000) semen antibody titers in men with evidence of genital tract inflammation greater than 10(6) white blood cells/ml semen; 3/5 versus 5/23, p greater than 0.1 Fisher exact test). All **HIV**-1 antibodies detected were of the IgG class; no **IgA** or IgM class antibodies of titers greater than or equal to 40 were found in either blood or semen. Thirteen paired blood and semen samples from individual patients were analyzed for antibody specificity by Western blot. In some cases antibody profiles in semen were different from those in blood; strong antibody reactivity against the **gp160** viral coat antigen band was consistently detected in semen and blood, whereas the prevalence of detectable antibody reactivity against the p55 and p17 **HIV**-1 antigen bands was significantly reduced in semen.(ABSTRACT TRUNCATED AT 250 WORDS)

L4 ANSWER 75 OF 99 MEDLINE on STN

92147874. PubMed ID: 1737846. **Human immunodeficiency virus** infection induces both polyclonal and virus-specific B cell activation. Shirai A; Cosentino M; Leitman-Klinman S F; Klinman D M. (Laboratory of Retrovirus Research, Food and Drug Administration, Bethesda, Maryland 20892.) Journal of clinical investigation, **(1992 Feb)** 89 (2) 561-6. Journal code: 7802877. ISSN: 0021-9738. Pub. country: United States. Language: English.

AB Peripheral blood lymphocytes (PBL) were obtained from **HIV**-1-infected patients at different stages of disease. The absolute number of IgM-, IgG-, and **IgA**-producing lymphocytes per 10(6) PBL was increased 2.8-, 3.4-, and 1.9-fold, respectively, compared with normal controls. 2-17% of IgG-secreting patient cells reacted with the **gp160 envelope** glycoprotein of **HIV**-1 (a 737-fold increase over background), while 1-9% reacted with p24 (140-fold over background). In addition to this **HIV**-specific B cell activation, the number of lymphocytes reactive with nonviral antigens such as DNA, myosin, actin, trinitrophenylated keyhole limpet hemocyanin, and ovalbumin was increased by a mean of 17.9-fold. Evidence suggests that the latter changes reflect an **HIV**-induced polyclonal B cell activation unrelated to the production of anti-**HIV** antibodies. For example, the proportion of IgG anti-**gp160**- and anti-p24-secreting lymphocytes declined in patients with advanced disease, whereas the number of B cells producing antibodies to non-**HIV** antigens rose. Moreover, CD4 cell count and T4/T8 ratio showed a significant inverse correlation with the degree of polyclonal activation but not with anti-**HIV** responsiveness. These observations demonstrate that both quantitative and qualitative changes in B cell activation accompany (and may be predictive of) disease progression in **HIV**-infected individuals.

L4 ANSWER 76 OF 99 MEDLINE on STN

92101607. PubMed ID: 1759500. SIV vaccines: current status. The role of the SIV-macaque model in AIDS research. Gardner M. (Department of Pathology, School of Medicine, University of California, Davis 95616.) Vaccine, **(1991 Nov)** 9 (11) 787-91. Ref: 41. Journal code: 8406899. ISSN: 0264-410X. Pub. country: ENGLAND: United Kingdom. Language: English.

AB SIV vaccines made of inactivated whole virus, modified live virus and native and recombinant **envelope** antigens have protected macaques against experimental infection with low doses of cell-free SIV given systemically. The few vaccinated monkeys that do become infected have tended to live longer than the infected controls. Protection against cell-associated virus has not as yet been tested. The recombinant **envelope** vaccines now on test have generally not been as effective as the whole virus vaccines. Post-infectious immunotherapy with SIV vaccines has been ineffective. The same whole virus and modified live virus vaccines that protect against systemic infection fail to protect against genital **mucosal** challenge with cell-free virus. Since sexual transmission is the major route of **HIV** spread on a global scale, a major effort is now required to develop vaccines in this animal model that induce genital **mucosal** as well as systemic immunity against infection with both cell-free and cell-associated SIV.

L4 ANSWER 77 OF 99 MEDLINE on STN

92087468. PubMed ID: 1370128. Mechanism of **HIV** spread from lymphocytes to epithelia. Phillips D M; Bourinbaiar A S. (Population Council, Center for Biomedical Research, New York, New York 10021.) Virology, **(1992 Jan)** 186 (1) 261-73. Journal code: 0110674. ISSN: 0042-6822. Pub. country: United States. Language: English.

AB Contact of **human immunodeficiency virus** (**HIV**)-infected MOLT-4 lymphocytes with epithelial cells derived from small intestine (I407; Intestine 407) resulted in a rapid polar budding of viral particles into

an enclosed space formed by interdigitating microvilli of the contacting cells. Electron microscopy showed that released **HIV** was taken up into the **mucosal** cell via three independent mechanisms: (1) phagocytosis, (2) coated pits, and (3) direct fusion. Morphological evidence suggests that internalized **HIV** may escape into the cytoplasm of the target cell by uncoating at the endosomal membrane. Based on CD4 antibody binding and CD4 antibody blocking experiments, **HIV** entry does not appear to be mediated by a viral CD4 receptor. Productivity of I407 infection was confirmed by virus isolation from cocultured MT-4 lymphocytic cells, reverse transcriptase assay, p24 antigen ELISA, in situ **HIV** mRNA hybridization, and Southern dot blot analysis. Contrary to infection with free virus, the cell-to-cell infection was not blocked by anti-**gp120** or antiviral serum from **HIV**-positive individuals. It appears that **HIV** transmission within the confined space between contacting cells enables **HIV** to evade immune protection provided by neutralizing antibodies. Our results reveal a mechanism of **HIV** infection of epithelial cells which is triggered by cell-cell contact. Furthermore, these observations offer an insight into the cellular sequence of events which may take place during sexual transmission of **HIV** across an intact epithelial barrier.

L4 ANSWER 78 OF 99 MEDLINE on STN

92060968. PubMed ID: 1659310. Simian and feline immunodeficiency viruses: animal lentivirus models for evaluation of AIDS vaccines and antiviral agents. Gardner M B. (Department of Medical Pathology, University of California, Davis 95616.) Antiviral research, **(1991 May)** 15 (4) 267-86. Ref: 82. Journal code: 8109699. ISSN: 0166-3542. Pub. country: Netherlands. Language: English.

AB Infection of captive macaques with simian immunodeficiency virus (SIV) and domestic cats with feline immunodeficiency virus (FIV), both discovered in the last five years, represent excellent animal models for infection of humans with the **human immunodeficiency virus** (**HIV**). Protection against challenge infection and protection against development of simian and feline acquired immunodeficiency syndrome has been achieved in each model by use of inactivated whole virus or virus-cell vaccines. A recombinant SIV **envelope** peptide vaccine has also proved efficacious. These vaccines have protected against 10-100 animal infectious doses of the homologous cell-free virus given systemically, and, in the simian model, apparently show cross protection against a heterologous strain of SIV. Protected animals appear free of any latent infection although late breakthroughs of infection in a few animals imply that not all vaccinated animals are completely protected. The mechanism of protection in the simian model apparently involves **envelope** antibody but the role of neutralizing antibody remains unclear. Questions remaining to be answered in both SIV and FIV models are: (1) the duration of immunity, (2) the extent of protection against heterologous strains and **mucosal** infection, (3) protection against infection with cell-associated virus and (4) the role, if any, of cellular immunity in vaccine protection. Initial attempts at post-infection immunotherapy with SIV vaccines have not yet been successful. The inactivated whole SIV and FIV vaccines offer a promising start and provide hope that a prophylactic AIDS vaccine will be developed. Use of these animal models for antiviral therapy is just now getting underway. Both models should prove especially useful for studies of prophylaxis and therapy, especially during the early stages of infection and for investigations on drug pharmacokinetics or toxicity that can not be done as well in **HIV**-infected humans. The animals will also be ideal for testing the pathogenicity of drug-induced mutant forms of SIV and FIV. For these purposes it will be necessary to create self-sustaining specific pathogen-free macaque and cat breeding colonies and provide increased housing facilities for infected animals. The future of AIDS research is crucially dependent on the long term availability of these animal models.

L4 ANSWER 79 OF 99 MEDLINE on STN

91370198. PubMed ID: 1892992. The interaction of salivary secretions with the human complement system--a model for the study of host defense systems on inflamed **mucosal** surfaces. Boackle R J. (Department of Microbiology and Immunology, College of Dental Medicine, Medical University of South Carolina, Charleston.) Critical reviews in oral biology and medicine : an official publication of the American Association of Oral Biologists, **(1991)** 2 (3) 355-67. Ref: 82. Journal code: 9009999. ISSN: 1045-4411. Pub. country: United States. Language: English.

AB When complement first contacts salivary secretions, as when gingival crevicular fluid first meets saliva at the gingival margin, complement function is enhanced. The immediate potentiation of the complement system at equal volume ratios of serum to saliva is due to several factors, including the lower ionic strength of saliva when compared with serum and the presence of certain salivary glyproteins such as the nonimmunoglobulin agglutinins that appear to simultaneously activate C1 and affect (sequester) certain complement control proteins, such as Factor H. This

initial potentiation of the complement cascade by saliva may aid in defending the area immediately above the gingival crevice from oral microbiota that are being coated with a combination of serous exudate components and salivary components. As serum becomes much more diluted with saliva (i.e., crevicular fluid moves away from the supragingival area), the acidic proline-rich salivary proteins (APRP) begin to disrupt the unbound C1q-C1r2-C1s2 macromolecular complexes. Thus, the APRP along with other C1 fixing substances in saliva appear to restrict complement function, but only when the ratios of saliva to serum exceed 250:1. Since certain salivary glycoproteins bind to viruses, the potentiation of the complement system by saliva may also play a role in neutralizing certain viral infections on **mucosal** surfaces where tissue transudates containing complement begin to contact **mucosal** secretions such as saliva. Again, the ratio of serous fluid to **mucosal** secretion appears to be an important factor. This article also discusses some of our preliminary data and speculations concerning the binding of the self-associating high-molecular-weight nonimmunoglobulin salivary agglutinins (NIA) with the **envelope** of the **human immunodeficiency virus** (**HIV**) and the possible cooperative role of C1q and fibronectin in aiding neutralization of **HIV** infectivity.

L4 ANSWER 80 OF 99 MEDLINE on STN

91293470. PubMed ID: 2065890. Mother-to-child transmission of **human immunodeficiency virus**. Rossi P; Moschese V. (Department of Immunology, Karolinska Institute, Stockholm, Sweden.) FASEB journal : official publication of the Federation of American Societies for Experimental Biology, **(1991 Jul)** 5 (10) 2419-26. Ref: 66. Journal code: 8804484. ISSN: 0892-6638. Pub. country: United States. Language: English.

AB Transmission of **HIV** virus from an infected mother to her offspring is becoming the leading cause of spreading in the pediatric population. This is particularly burdensome in the pattern II countries where **HIV** infection has reached epidemic proportions and infection rates affect more women of childbearing age than men. During the last few years considerable effort has been directed at defining the optimal methods for identifying infants of **HIV**-infected mothers who will themselves prove to be infected because conventional serological assessment is impaired due to placental transfer of maternal IgG. At present, detection of specific **IgA** to **HIV** proteins, evaluation of autochthonous antibody production in vitro from infants' lymphocytes, and gene amplification of **HIV** DNA/RNA by polymerase chain reaction are the most promising procedures for early diagnosis within the first 6 months of life. Nevertheless all these techniques are cumbersome when evaluating specimens from the newborn child. Many studies have been performed to identify those maternal factors affecting the risk of vertical transmission. So far, none of them has shown real prognostic value. However, evaluation of maternal antibody response to functional epitopes of **HIV envelope** proteins such as the principal neutralizing domain, in some epidemiological settings, seems to correlate to a reduced rate of mother-to-child transmission.

L4 ANSWER 81 OF 99 MEDLINE on STN

91220713. PubMed ID: 1708933. Homotypic antibody responses to fresh clinical isolates of **human immunodeficiency virus**. Montefiori D C; Zhou I Y; Barnes B; Lake D; Hersh E M; Masuho Y; Lefkowitz L B Jr. (Department of Pathology, Vanderbilt University Medical School, Nashville, Tennessee 37232.) Virology, **(1991 Jun)** 182 (2) 635-43. Journal code: 0110674. ISSN: 0042-6822. Pub. country: United States. Language: English.

AB **Human immunodeficiency virus** type 1 (**HIV**-1) exhibits extensive genomic and antigenic diversity, which is thought to contribute to the failure of the host's immune response to control infection and prevent clinical progression. Part of this failure may be due to utilization by the virus of antigenic variation as a means to escape protective immune responses. Antibody-escape variants of **HIV**-1 were studied here using fresh clinical isolates and autologous plasmas. **HIV**-1 was isolated from the plasma of seven people who were all seropositive for at least 2 years, and symptomatic sometime during that period. Isolated viruses were confirmed as **HIV**-1 by the presence of reverse transcriptase activity in infected culture supernatants, and by positive immunofluorescence using human monoclonal antibody to **HIV**-1 core protein. Plasma from these people were positive by Western immunoblot (DuPont) for most major **HIV**-1 (strain IIIB) antigens. These plasmas neutralized three laboratory strains of **HIV**-1 (i.e., IIIB, RF, and MN) but did not neutralize the homotypic strain in five cases, and had greatly reduced neutralizing titers against the homotypic strain in two cases. Homotypic neutralizing antibodies were absent in autologous plasma obtained 3 months later. When antibody titers were measured by fixed-cell indirect immunofluorescence assays (IFAs), high titers of IgG (1:6400 to 1:25,600) were detected against **HIV**-1 IIIB, while low titers of only 1:20 to 1:160 were detected against homotypic viral antigens at the time of virus isolation, and remained low 12 and 16 weeks later. No class **IgA**, IgD, IgE, or IgM

antibodies to homotypic viral antigens, as possible IgG-blocking antibodies, were detected by fixed-cell IFAs. Cross-reactions with heterologous donor's plasmas were observed in some cases, and in these cases the cross-reactions were unidirectional. Live-cell IFAs detected IgG in patient's plasma to **HIV**-1 IIIB-infected cells but not to cells infected with homotypic isolates. These results suggest that it is common for neutralization-resistant **HIV**-1 variants to appear during the course of infection, and that all or most antigens of these variants are capable of escaping antibody recognition.

L4 ANSWER 82 OF 99 MEDLINE on STN

91154987. PubMed ID: 1705583. Detection of infection with **human immunodeficiency virus** (**HIV**) type 1 in infants by an anti-**HIV** immunoglobulin A assay using recombinant proteins. Martin N L; Levy J A; Legg H; Weintrub P S; Cowan M J; Wara D W. (Department of Pediatrics, University of California, San Francisco 94143.) Journal of pediatrics, **(1991 Mar)** 118 (3) 354-8. Journal code: 0375410. ISSN: 0022-3476. Pub. country: United States. Language: English.

AB To diagnose infection with the **human immunodeficiency virus** (**HIV**) soon after birth in infants born to **HIV** type 1-infected women, we developed antiviral **IgA** Western blot and dot blot assays with recombinant **HIV**-1 proteins. Thirty-three infants born to **HIV**-1-seropositive mothers and nine infants born to **HIV**-1-seronegative intravenous drug-abusing mothers were followed prospectively. Infection was documented by positive virus culture. Results with the polymerase chain reaction were used for comparison. Twelve infants were found infected with **HIV**-1; the earliest age at which cultures became positive ranged from birth to 31 weeks of age. Of the 12 culture-positive infants, 10 had anti-**HIV IgA** antibodies detectable initially between birth (cord blood) and 27 weeks of age. Anti-**HIV IgA** was not present in the uninfected infants or in the control subjects, either by Western blot or dot blot assays. Testing for anti-**HIV IgA** antibodies with recombinant **HIV**-1 proteins is an effective method for detecting viral infection in newborn and young infants.

L4 ANSWER 83 OF 99 MEDLINE on STN

90376271. PubMed ID: 2204698. Salivary antibodies to **human immunodeficiency virus** type 1 in a phase I AIDS vaccine trial. Archibald D W; Hebert C A; Sun D; Tacket C O. (Department of Oral Pathology, Dental School, University of Maryland, Baltimore 21201.) Journal of acquired immune deficiency syndromes, **(1990)** 3 (10) 954-8. Journal code: 8812597. ISSN: 0894-9255. Pub. country: United States. Language: English.

AB **HIV**-1-specific secretory antibodies may be a desirable outcome in individuals receiving AIDS vaccines. We investigated parotid and whole saliva samples for **HIV**-specific antibodies collected from five volunteers who received a recombinant **HIV**-1 **envelope** glycoprotein (rgp160) vaccine. Ten healthy, adult volunteers received intramuscularly either three doses of rgp160 (40 or 80 micrograms), a hepatitis B vaccine, or a placebo on days 0, 30, and 180. Saliva samples were collected on days 0, 28, 60, 120, 194, and 270 from the volunteers. All volunteers were negative for serum **HIV** antibodies by ELISA (Abbott). By Western blotting, serum antibodies to **envelope** antigens were demonstrated in one of three individuals who received the low dose vaccine and two of two who received the high dose. Antibodies to **gp160** were detected in whole saliva on day 194 from one of these individuals by Western blotting. Parotid saliva collected on all dates did not contain detectable **HIV**-specific antibodies. The finding of **HIV**-1-specific antibodies in whole saliva following vaccination may indicate that development of **mucosal** immunity is possible.

L4 ANSWER 84 OF 99 MEDLINE on STN

90364282. PubMed ID: 2392618. **HIV**-specific **IgA** antibodies in tears of children with AIDS or at risk of AIDS. Renom G; Bouquety J C; Lanckriet C; Georges A J; Siopathis M R; Martin P M. (Institut Pasteur, Bangui.) Research in virology, **(1990 May-Jun)** 141 (3) 355-63. Journal code: 8907469. ISSN: 0923-2516. Pub. country: France. Language: English.

AB To improve on the diagnosis of **human immunodeficiency virus** (**HIV**) infection, 14 children with clinical evidence of AIDS, 86 children less than 15 months old and born to seropositive mothers, and 29 controls were tested for the presence of **IgA** antibody in tears directed against **HIV** antigens on Western blots. **IgA** antibodies in tears against **env**- and pol-encoded proteins were present in 13 of 14 children with AIDS and in 13 of 86 children born to seropositive mothers. No **HIV**-specific **IgA** was observed in tears of the 29 controls. Among the 86 children less than 15 months old, 11 had clinical evidence of AIDS and 7 of them (64%) had **HIV**-specific **IgA** in tears. Results show that the demonstration of lacrimal **HIV**-specific **IgA** may help to distinguish between truly infected children and those whose **HIV** antibodies are passively

transferred from the mother. Therefore, this simple method is a good tool for laboratory diagnosis of paediatric AIDS.

L4 ANSWER 85 OF 99 MEDLINE on STN
90321488. PubMed ID: 2196908. Detection of salivary immunoglobulin A antibodies to **HIV**-1 in infants and children. Archibald D W; Johnson J P; Nair P; Alger L S; Hebert C A; Davis E; Hines S E. (Department of Oral Pathology, University of Maryland, Baltimore 21201.) AIDS (London, England), **(1990 May)** 4 (5) 417-20. Journal code: 8710219. ISSN: 0269-9370. Pub. country: United States. Language: English.
AB Secretory immunoglobulin A (slgA) antibodies of non-maternal origin are present in newborns and slgA to **HIV**-1 antigens has been detected in infected adults. In this study we investigated the presence of **HIV**-1-specific **IgA** in saliva from 41 children (aged 1 day-46 months) born to women at risk for **HIV**-1 infection. Saliva samples were assayed for **HIV**-1 antibodies with **IgA**-specific Western blot. The samples from 10 out of 11 children with subsequently proven infection, including one aged 6 months, demonstrated **IgA** antibodies to **HIV**-1 **envelope** antigens. Samples from infants under 15 months, who were born to infected mothers and subsequently shown to be uninfected, were slgA negative. Of the 12 children with continued indeterminate **HIV**-1 status, eight showed neither slgA nor serologic evidence of infection and four showed slgA antibodies. **HIV**-1-specific slgA was detectable before the age of 15 months and may prove to be valuable in the diagnosis of **HIV**-1 infection in infants.

L4 ANSWER 86 OF 99 MEDLINE on STN
90251393. PubMed ID: 2339025. Antibodies to **human immunodeficiency virus** in the breast milk of healthy, seropositive women. Belec L; Bouquety J C; Georges A J; Siopathis M R; Martin P M. (Institut Pasteur de Bangui, Central African Republic.) Pediatrics, **(1990 Jun)** 85 (6) 1022-6. Journal code: 0376422. ISSN: 0031-4005. Pub. country: United States. Language: English.
AB Reports of rare cases of suspected transmission of the **human immunodeficiency virus** (**HIV**) from mother to children by breast milk have been recently published. To study the factors that possibly limit **HIV** transmission through breast-feeding, milk samples obtained from 15 healthy, seropositive mothers and 4 seronegative control subjects were studied for the presence of anti-**HIV** antibodies. All samples from seropositive women contained IgG antibody against **envelope** glycoproteins **gp160** and/or **gp120**, and 11 of 15 samples contained **IgA** antibodies against **gp160**. **IgA** antibodies against other viral antigens were more rarely recovered, except against the internal proteins of the virus, p18 and p25. The finding of **IgA** antibodies to **HIV**-1 in breast milk establishes that the virus elicits a local immune response in heterosexual, seropositive women. The role of local antibodies in the postnatal transmission of **HIV** remains to be determined.

L4 ANSWER 87 OF 99 MEDLINE on STN
90220200. PubMed ID: 1970106. Early diagnosis of **HIV** infection in infants by detection of **IgA HIV** antibodies. Weiblen B J; Lee F K; Cooper E R; Landesman S H; McIntosh K; Harris J A; Nesheim S; Mendez H; Pelton S I; Nahmias A J; +. (Massachusetts Department of Public Health, State Laboratory Institute, Boston.) Lancet, **(1990 Apr 28)** 335 (8696) 988-90. Journal code: 2985213R. ISSN: 0140-6736. Pub. country: ENGLAND: United Kingdom. Language: English.
AB With the aim of achieving earlier diagnosis of **human, immunodeficiency virus** (**HIV**) infection in infants, **IgA** and IgM **HIV** antibodies in serum samples from babies born to seropositive mothers were assayed by immunoblot and enzyme-linked immunosorbent assay after removal of IgG with recombinant protein G. 64 samples were from 38 **HIV**-infected babies with Centers for Disease Control classifications of P1 or P2. Among these infected children **IgA HIV** antibodies were present in all 23 samples from those older than 12 months, in 12 of 18 samples from babies aged 6-12 months, in 5 of 10 samples from babies aged 3-5 months, and in 2 of 13 from babies under 3 months old. The 6 **IgA**-negative samples from infants over 6 months were all from infants with severe AIDS and/or hypogammaglobulinaemia. **IgA HIV** antibodies were present in twice as many samples as IgM **HIV** antibodies (66% vs 33%). No IgM or **IgA HIV** antibodies were detected in infants who subsequently seroreverted or in infants born to seronegative mothers. The correlation of the serological results with clinical information on each child suggests that detection of **IgA HIV** antibodies is an effective method for early diagnosis of **HIV**-infected infants without signs of infection.

L4 ANSWER 88 OF 99 MEDLINE on STN
90066784. PubMed ID: 2586676. [**HIV** occupational risk of surgical specialists and operating room personnel in the Saint Lucas Hospital in Amsterdam]. **HIV**-beroepsrisico van snijdende specialisten en

operatiekamermedewerkers in het Sint Lucas Ziekenhuis te Amsterdam. Leentvaar-Kuijpers A; Keeman J N; Dekker E; Dekker M M; Ansink-Schipper M C; Coutinho R A. Nederlands tijdschrift voor geneeskunde, **(1989 Dec 2)** 133 (48) 2388-91. Journal code: 0400770. ISSN: 0028-2162. Pub. country: Netherlands. Language: Dutch.

AB All instrument and needle accidents, and **mucosal** exposure to blood involving surgical specialists and operating room personnel were recorded for a seven-month period in a middle-sized Amsterdam hospital, the St. Lucas. Fifty-four accidents were reported, of which 42 were percutaneous wounds and 12, blood splatters in the eyes. The frequency of percutaneous wounds per operation per person ranged from 0 to 0.013. In the same period 3098 patients who had to be operated on were asked to participate in an anonymous study for **HIV** antibody. One hundred and twenty patients refused participation (3.9%). Of the 2978 participating patients seven were seropositive for anti-**HIV** (0.23%). The observed percutaneous accident frequency and **HIV** prevalence were used in combination with reports from the literature on the risk of infection after a single exposure to **HIV** infected material, to calculate the **HIV** professional risk for operating room personnel in this hospital. For general surgeons the risk of infection (based on 500 operations per year) was calculated as 0.0012 for an occupational lifespan of 30 years. For the other specialists and functions the risk was the same or less. Considering the low risk our conclusion is that screening of preoperative patients is not necessary in this hospital. The observance of general protective measures provides sufficient protection for the professional group examined.

L4 ANSWER 89 OF 99 MEDLINE on STN

90030168. PubMed ID: 2680057. Mycobacterial disease, immunosuppression, and acquired immunodeficiency syndrome. Collins F M. (Trudeau Institute, Inc., Saranac Lake, New York 12983.) Clinical microbiology reviews, **(1989 Oct)** 2 (4) 360-77. Ref: 214. Journal code: 8807282. ISSN: 0893-8512. Pub. country: United States. Language: English.

AB The mycobacteria are an important group of acid-fast pathogens ranging from obligate intracellular parasites such as Mycobacterium leprae to **environmental** species such as M. gordonae and M. fortuitum. The latter may behave as opportunistic human pathogens if the host defenses have been depleted in some manner. The number and severity of such infections have increased markedly with the emergence of the acquired immunodeficiency syndrome (AIDS) epidemic. These nontuberculous mycobacteria tend to be less virulent for humans than M. tuberculosis, usually giving rise to self-limiting infections involving the cervical and mesenteric lymph nodes of young children. However, the more virulent serovars of M. avium complex can colonize the bronchial and intestinal **mucosal** surfaces of healthy individuals, becoming virtual members of the commensal gut microflora and thus giving rise to low levels of skin hypersensitivity to tuberculins prepared from M. avium and M. intracellulare. Systemic disease develops when the normal T-cell-mediated defenses become depleted as a result of old age, cancer chemotherapy, or infection with **human immunodeficiency virus**. As many as 50% of **human immunodeficiency virus** antibody-positive individuals develop mycobacterial infections at some time during their disease. Most isolates of M. avium complex from AIDS patients fall into serotypes 4 and 8. The presence of these drug-resistant mycobacteria in the lungs of the AIDS patient makes their effective clinical treatment virtually impossible. More effective chemotherapeutic, prophylactic, and immunotherapeutic reagents are urgently needed to treat this rapidly increasing patient population.

L4 ANSWER 90 OF 99 MEDLINE on STN

90000746. PubMed ID: 2506903. Frequent detection of **HIV**- and IgG-specific IgM and **IgA** antibodies in **HIV**-positive cord-blood sera: fine analysis by western blot. Schupbach J; Wunderli W; Kind C; Kernen R; Baumgartner A; Tomasik Z. (Swiss National Center for Retroviruses, University of Zurich.) AIDS (London, England), **(1989 Sep)** 3 (9) 583-9. Journal code: 8710219. ISSN: 0269-9370. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Cord-blood sera of 36 babies born to **HIV**-positive mothers in Switzerland were tested for immunoglobulin (Ig) M or **IgA** by **HIV** Western blot. IgM was found in 28, and **IgA** in 19 of unabsorbed sera. Preabsorption with immobilized protein A or G was used to remove IgG, which allowed differentiation between **HIV**-specific and IgG-specific IgM or **IgA**. Protein G proved superior and showed that 30% of 23 sera had **HIV**-specific IgM, while 48% had **HIV**-specific **IgA**. **HIV**-specific IgM and/or **IgA** was found in 13 out of 21 cases (62%); four out of 21 (19%) had both. **HIV**-specific IgM reacted most frequently with pol or **env** proteins, while **HIV**-specific **IgA** reacted more frequently with gag than pol; no **IgA** were directed against **env** proteins. IgG-specific IgM and **IgA**, mostly at gag bands, were present in 83 and 38%, respectively. Thus, a large percentage of children born to **HIV**-positive mothers have **HIV**-specific **IgA** and/or IgM which can be distinguished

from IgG-specific **IgA** or IgM, which is also present in the majority of such children. Future studies will have to show whether these antibodies are of diagnostic relevance.

L4 ANSWER 91 OF 99 MEDLINE on STN
89374566. PubMed ID: 3509678. Antibodies to HTLV-1 in saliva of seropositive individuals from Japan. Archibald D; Essex M; McLane M F; Sauk J; Tachibana N; Mueller N. (Department of Oral Pathology, Dental School, University of Maryland, Baltimore.) Viral immunology, **(1987-88)** 1 (4) 241-6. Journal code: 8801552. ISSN: 0882-8245. Pub. country: United States. Language: English.
AB Secretory antibodies protect **mucosal** surfaces against transmission of many viruses. Human T-lymphotropic Virus, Type I (HTLV-I) is transmitted via blood products and via sexual contact across **mucosal** surfaces. We investigated the presence of HTLV-I-specific antibodies in whole saliva samples from 10 seronegative and 28 seropositive volunteers from a hospital in southern Japan. Antibodies directed to HTLV-I antigens were found in the salivas from 22 of 28 (79%) of the seropositive subjects. None of the seronegative individuals showed evidence of salivary antibodies. Antibodies directed to the **envelope** antigens of the virus were found in 21 of 22 positive saliva samples. Secretory antibodies may be important in preventing **mucosal** transmission.

L4 ANSWER 92 OF 99 MEDLINE on STN
89341492. PubMed ID: 2760496. Antibodies to **human immunodeficiency virus** in vaginal secretions of heterosexual women. Belec L; Georges A J; Steenman G; Martin P M. (Institut Pasteur, Bangui, Central African Republic.) Journal of infectious diseases, **(1989 Sep)** 160 (3) 385-91. Journal code: 0413675. ISSN: 0022-1899. Pub. country: United States. Language: English.
AB To study the local immune response to **human immunodeficiency virus** type 1 (**HIV**-1) in women infected by or exposed to **HIV**-1, 75 women were studied: 15 were IgG-seropositive but clinically asymptomatic, 15 had acquired immune deficiency syndrome (AIDS), 15 were IgG-seronegative with seropositive husbands, and 30 were healthy seronegative women who were selected as controls. Serum samples and vaginal secretions were tested for antibodies to **HIV**-1 IgG and **IgA** by Western blot analysis. Antibodies of the IgG and **IgA** classes were detected in serum samples and vaginal secretions from healthy seropositive women and from women with AIDS. Local IgG antibodies to all viral proteins were detected by Western blot tests. Genital **IgA** antibodies were mainly directed to the core proteins p18 and p25, the p68 reverse transcriptase, and the **gp160** and **gp41** glycoproteins; **IgA** antibodies to the glycoprotein **gp120** were rarely recovered. Antibodies of both the IgG and **IgA** classes in genital secretions were directed to all viral proteins, including surface glycoproteins, and could play a role in limiting the virus infectivity on normal mucosa.

L4 ANSWER 93 OF 99 MEDLINE on STN
89221956. PubMed ID: 2711041. Antibodies to HIV2 in genital secretions. Belec L; Peghini M; Georges A J; Barabe P; Martin P M. (Institut Pasteur de Bangui, Dakar.) Research in virology, **(1989 Jan-Feb)** 140 (1) 15-21. Journal code: 8907469. ISSN: 0923-2516. Pub. country: France. Language: English.
AB In order to study the local immune response to HIV2, three exclusively heterosexual, infected West African patients were selected: one male with full blown AIDS, one female with ARC and one healthy HIV2-carrier female. Sera and genital secretions were obtained and tested for anti-HIV2 IgG and **IgA** antibodies by Western blotting. In semen and in vaginal secretions, IgG antibodies directed against all viral antigens were detected. In comparison with the IgG response, local **IgA** antibody response was less intense and heterogenous. Two out of 3 patients had local antibodies of the **IgA** class directed against the **envelope** glycoprotein GP105. Such antibodies of both the IgG and **IgA** classes in genital secretions could play a protective role in heterosexual transmission of HIV2.

L4 ANSWER 94 OF 99 MEDLINE on STN
89120146. PubMed ID: 2914443. Admission of AIDS patients to a medical intensive care unit: causes and outcome. Rogers P L; Lane H C; Henderson D K; Parrillo J; Masur H. (Critical Care Medicine Department, National Institute of Allergy and Infectious Disease, Bethesda, MD.) Critical care medicine, **(1989 Feb)** 17 (2) 113-7. Journal code: 0355501. ISSN: 0090-3493. Pub. country: United States. Language: English.
AB As the number of cases of AIDS increases, it is important to determine whether ICUs can be productively and safely used for this patient population. From July 1981 to March 1987, 216 patients were admitted to the medical ICU: 166 (77%) were admitted for procedures and 50 (23%) were admitted for life-sustaining support. Most of the patients were admitted for respiratory failure (36 of 50), primarily as a result of Pneumocystis

carinii pneumonia. Other patients were admitted for cardiovascular instability (six of 50 patients), CNS dysfunction (four patients), or other reasons (four patients). Of 50 patients admitted to the ICU, 13 (26%) were alive 3 months after hospital discharge. Despite 25 needle-stick injuries and 56 **mucosal** splashes involving **human immunodeficiency virus** (**HIV**)-infected patients and staff, no staff member converted **HIV** serology. These results suggest that AIDS patients may benefit from ICU admission. These patients appear to pose a low risk to the hospital staff in terms of occupationally acquired **HIV** infection, but strong emphasis needs to be placed on minimizing accidental exposures to potentially infected body fluids and to adhering to universal precautions.

L4 ANSWER 95 OF 99 MEDLINE on STN

89007054. PubMed ID: 3049355. Perspectives on gastrointestinal infections in AIDS. Janoff E N; Smith P D. (Department of Medicine, Veterans Administration Medical Center, Minneapolis, Minnesota.) Gastroenterology clinics of North America, **(1988 Sep)** 17 (3) 451-63. Ref: 91. Journal code: 8706257. ISSN: 0889-8553. Pub. country: United States. Language: English.

AB Gastrointestinal illnesses are among the most common and debilitating complication of infections with **HIV**, affecting 50 per cent to almost 100 per cent of AIDS patients in developed and developing countries, respectively. A number of factors including relevant modes of transmission, the **environment**, and immunosuppression conspire to determine which enteric infectious agents **HIV**-infected persons acquire. In developed countries, transmission of a diverse spectrum of bacteria, viruses, and protozoa is facilitated by unprotected receptive anal intercourse and anal-lingual contact among homosexual men with multiple partners. In developing countries, where most **HIV** infections occur among heterosexual persons, waterborne and foodborne transmission are the principal modes of transmission of enteric organisms. The severity and duration of symptoms associated with enteric pathogens are determined by the host's immunologic response to the organism. Candida albicans often causes local **mucosal** disease but less often causes systemic infections in **HIV**-infected persons, likely because polymorphonuclear cell function is intact. The ability of AIDS patients to control infections with G. lamblia and C. jejuni is related to their ability to mount an antibody response to these organisms during infection. The virulence of the organism may also affect the clinical response to infection. Cryptosporidium causes diarrheal symptoms in both immunocompetent and AIDS patients, but illness is more severe and prolonged in the latter. Giardia lamblia and C. jejuni infections are associated with a range of clinical manifestations in both AIDS patients and **HIV**-seronegative persons, whereas CMV and possibly adenovirus appear to cause significant disease only among immunocompromised subjects. The availability of effective therapy is among the most decisive factors in determining the duration of enteric infections in AIDS patients. For example, Giardia lamblia may cause acute abdominal pain and diarrhea in **HIV**-infected subjects but prolonged infections with the parasite are uncommon because effective therapy is available. In contrast, infections with CMV and Cryptosporidium may be severe and chronic as available therapy is generally ineffective or only transiently effective. Awareness of these clinical, epidemiologic, immunologic, and therapeutic aspects of gastrointestinal illness in **HIV**-infected subjects should help to direct the diagnostic evaluation of these patients and to direct areas of research.

L4 ANSWER 96 OF 99 MEDLINE on STN

88301529. PubMed ID: 3165484. [Virus-specific antibody profile in various stages of **HIV**-1 infection. Western blot analysis of 170 patients]. Das erregerspezifische Antikorperprofil in den verschiedenen Stadien der **HIV**-1-Infektion. Western Blot Analyse von 170 Patienten. Schulte C; Meurer M; Braun-Falco O; Held M; Froschl M. (Dermatologische Klinik und Poliklinik, Ludwig-Maximilians-Universitat Munchen.) Klinische Wochenschrift, **(1988 Jun 1)** 66 (11) 488-93. Journal code: 2985205R. ISSN: 0023-2173. Pub. country: GERMANY, WEST: Germany, Federal Republic of. Language: German.

AB The western blot analysis of 170 patients with **HIV**-1-infection demonstrated that 47% of the patients in latent stage, 58% of the patients with lymphadenopathy-syndrome and only 25% of the patients with the full-blown picture of AIDS showed the complete pattern of **HIV**-specific antibody response. This antibody response is mainly directed against the **env**-encoded **envelope** proteins **gp160**, **gp120** and **gp41**, against the gag-encoded core proteins p55, p24 and p17 as well as against the pol-encoded enzymatic proteins p66, p51 and p31. Antibodies against **gp160** and **gp120** were present in nearly all patients, whereas the prevalence of the other antibodies decreased with the stage of the disease. Statistical significant differences were found particularly

between patients with LAS or AIDS respectively. Antibodies against p17 were detected in 74% of the patients with LAS but only in 25% of the patients with AIDS. The lack of antibodies against p17, p24 or p51 was significantly associated with lower mean CD4/CD8-ratios (p less than 0.007) and higher mean serum levels of **IgA** (p less than 0.001) and beta-2-microglobulin (p less than 0.001). One third of the patients with LAS and this reduced pattern of antibody response developed AIDS within six months. These results demonstrate that the detection of antibodies against p17, p24 or p51 is of prognostic importance. A serological profile which lacks the antibody response against at least two of those three viral antigens indicates a progression of the disease activity.

L4 ANSWER 97 OF 99 MEDLINE on STN

88209353. PubMed ID: 3163253. Isotypic restriction of the antibody response to **human immunodeficiency virus**. Khalife J; Guy B; Capron M; Kieny M P; Ameisen J C; Montagnier L; Lecocq J P; Capron A. (Centre d'Immunologie et de Biologie Parasitaire, Institut Pasteur, Lille, France.) AIDS research and human retroviruses, **(1988 Feb)** 4 (1) 3-9. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.

AB **HIV**-infected individuals progress toward AIDS despite the early elicitation of a specific immune response. Analysis of the isotypic distribution of **HIV**-specific antibodies appears of special interest for two reasons: first, isotypic diversity is partly under the control of antigen-specific T-helper cells, the very cells infected by **HIV**; second, isotype determines antibody functions, effector (neutralization, antibody-dependent complement, or cell-mediated cytotoxicity) as well as blocking functions. We have investigated by Western blot analysis the isotypic profile of the antibody response to **HIV** structural proteins (**env**, gag, pol) and to the nonstructural protein F (3' orf), which is absent from the virion and might primarily target infected cells. In 115 asymptomatic individuals, infected by sexual contact (homosexual men) or intravenously (hemophiliacs), the response to gag-products was polyisotypic, including IgM, IgG1, IgG3 and **IgA**; the response to F was more restricted (IgM, IgG1, **IgA**) and the response to **env** strikingly restricted to the IgG1 isotype, suggesting different regulatory mechanisms in the B-cell response to these proteins. The isotypic distribution was also influenced by the route of infection, IgG4 and IgE (gag-specific) being exclusively elicited in the hemophiliac group. Finally, observations of potential diagnostic interest were made in a limited number of at-risk individuals; these included the presence of gag- and pol-specific IgM or **IgA** in the absence of any **HIV**-specific IgG isotypes; and the presence of gag- and F-specific antibodies in the absence of **env**-specific antibodies, suggesting the early occurrence of both isotypic and antigenic selection mechanisms during the course of **HIV** infection.

L4 ANSWER 98 OF 99 MEDLINE on STN

88186403. PubMed ID: 3162727. [Prognostic significance of antibodies to **HIV** nuclear proteins in patients with the lymphadenopathy syndrome]. Prognostische Bedeutung von Antikorpern gegen **HIV**-Kernproteine bei Patienten mit Lymphadenopathie-Syndrom. Schulte C; Meurer M; Froschl M. (Dermatologische Klinik und Poliklinik, Ludwig-Maximilians-Universitat Munchen.) Der Hautarzt; Zeitschrift fur Dermatologie, Venerologie, und verwandte Gebiete, **(1988 Jan)** 39 (1) 45-8. Journal code: 0372755. ISSN: 0017-8470. Pub. country: GERMANY, WEST: Germany, Federal Republic of. Language: German.

AB A total of 219 sera from **HIV**-infected patients were tested by a competitive immunoassay for the presence of antibodies to **env** and core protein. Whereas antibodies to the **HIV envelope** protein (**gp41**) were detected in all patients, only 84% of the patients with latent infection, 73% of the patients with LAS and 48% of the patients with AIDS had antibodies to the core protein (p 24). The prognostic importance of the decline of antibody reactivity to **HIV** core protein was further investigated in patients with lymphadenopathy syndrome or AIDS-related complex and correlated with other serological and immunological parameters. In those patients with no detectable anti-core reactivity, we found more frequently pathological and significantly higher serum levels of beta-2-microglobulin and **IgA**, but significantly lower numbers of leucocytes and lymphocytes and T4/T8 ratio than in patients with both **gp41 env** and p24 core antibodies. These results demonstrate that the determination of antibodies to **HIV** core proteins in sera of **HIV**-infected patients, especially with lymphadenopathy syndrome or AIDS-related complex, appears to be of great value for monitoring prognosis and disease activity.

L4 ANSWER 99 OF 99 MEDLINE on STN

86132010. PubMed ID: 3484980. Antibodies to human T-lymphotropic virus type III (HTLV-III) in saliva of acquired immunodeficiency syndrome (AIDS)

patients and in persons at risk for AIDS. Archibald D W; Zon L; Groopman J E; McLane M F; Essex M. Blood, **(1986 Mar)** 67 (3) 831-4. Journal code: 7603509. ISSN: 0006-4971. Pub. country: United States. Language: English.

AB Whole saliva samples collected from available people at risk in Boston for infection with human T-lymphotropic virus type III (HTLV-III/LAV), from late 1984 through early 1985, were analyzed for the presence of antibodies to viral proteins. Fourteen of 20 (70%) acquired immunodeficiency syndrome (AIDS) patients and 14 of 15 (93%) AIDS-related complex (ARC) patients had salivary antibodies that reacted with the virus-encoded glycoproteins **gp160** and **gp120** of HTLV-III infected cells. All of the AIDS and ARC patients had serum antibodies to the same antigens. Of 20 sex partners of AIDS/ARC patients, nine (45%) showed anti-HTLV-III antibodies, and four of 18 (22%) healthy homosexual males also were positive for such antibodies. Serum and salivary antibody status were the same in these groups. A minority of those patients positive for salivary antibodies to **env** gene-encoded **gp160** and **gp120** also had salivary antibodies to gag gene-encoded proteins of 55,000, 24,000, and/or 17,000 daltons. Immunoglobulin A (**IgA**) class antibodies comprised the majority of the salivary antibody response. The spectrum of HTLV-III proteins detected by the salivary and serum antibodies was similar. The possibility that secretory **IgA** from the gut-associated lymphoid system may play a role to restrict salivary transmission of HTLV-III should be considered.

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     (FILE 'HOME' ENTERED AT 11:40:40 ON 22 AUG 2005)

     FILE 'MEDLINE' ENTERED AT 11:41:54 ON 22 AUG 2005
L1        155517 S (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L2          1953 S L1 AND (MUCOSAL OR IGA)
L3           420 S L2 AND (ENV? OR GP160 OR GP120 OR GP41)
L4            99 S L3 AND PY<1997

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         50481 NEUTRALIZ?
L5           22 L4 AND NEUTRALIZ?

=> d l5,cbib,ab,1-22
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L5 ANSWER 1 OF 22 MEDLINE on STN

96424754. PubMed ID: 8827215. Protection against **mucosal** SIVsm challenge in macaques infected with a chimeric SIV that expresses **HIV** type 1 **envelope**. Quesada-Rolander M; Makitalo B; Thorstensson R; Zhang Y J; Castanos-Velez E; Biberfeld G; Putkonen P. (Swedish Institute for Infectious Disease Control, Karolinska Institute, Stockholm, Sweden.) AIDS research and human retroviruses, **(1996 Jul 20)** 12 (11) 993-9. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.

AB In a monkey model we used a chimeric SIV expressing the **HIV**-1 **envelope** gene (SHIV-4) as a live attenuated vaccine and a virulent SIVsm as a **mucosal** challenge. Four cynomolgus monkeys were inoculated intravenously with SHIV-4. Virus was repeatedly isolated from blood mononuclear cells of all four animals for 2 to 7 months after the inoculation of SHIV. All monkeys developed **neutralizing** antibodies to **HIV**-1 and high antibody titers to **HIV**-1 **envelope** glycoproteins. In contrast, no **neutralizing** antibodies to SIVsm were detected and cross-reacting antibodies to SIV **envelope** glycoproteins were demonstrable in low titers. Nine to 12 months after the SHIV inoculation the four monkeys and six naive control monkeys were challenged intrarectally with 10 monkey infectious doses of macaque cell-grown SIVsm. After a follow-up period of 1 year, two of four SHIV-infected monkeys were completely protected against SIVsm infection as shown by repeated negative virus isolations and negative polymerase chain reaction for SIV **envelope** DNA. One naive monkey that received blood from the two protected monkeys showed no signs of infection. The remaining two SHIV-infected monkeys showed an initial infection on challenge with SIVsm, but viral replication was thereafter suppressed. Cytotoxic T lymphocytes to SIV Nef and RT were demonstrable in one of four SHIV-infected monkeys before SIVsm challenge, but this monkey was not protected against SIV infection. All six control animals yielded virus repeatedly after SIVsm challenge and three of them showed declining CD4 cell counts. Thus, infection with SHIV expressing **HIV**-1 **envelope** could induce cross-protection against **mucosal** SIVsm challenge.

L5 ANSWER 2 OF 22 MEDLINE on STN

96415933. PubMed ID: 8818840. Strategies for AIDS vaccines. Stott E J; Schild G C. (National Institute for Biological Standards and Control

Potters Bar, Hertfordshire, UK.) Journal of antimicrobial chemotherapy, **(1996 May)** 37 Suppl B 185-98. Ref: 67. Journal code: 7513617. ISSN: 0305-7453. Pub. country: ENGLAND: United Kingdom. Language: English.

AB In the global AIDS epidemic, over half of all infections have occurred in people less than 25 years old resulting in profound social, economic and demographic consequences. Current estimates indicate that the present 15 million **HIV** infections will increase to over 30 million by the end of the millennium. For most countries a safe and effective vaccine offers the only hope of controlling the spread of this disease. The development of an effective vaccine against **HIV** is beset with formidable obstacles. Despite these difficulties, substantial progress has been made towards developing effective strategies for vaccination. Human clinical trials and animal models for AIDS, particularly simian immunodeficiency virus (SIV) infection of macaques, have proved invaluable in this quest. Inactivated virus vaccines induced potent protection in this model, but subsequent studies revealed that protection was mediated by antibody to cellular proteins present in the vaccine preparations and on the surface of infecting virions. This surprising observation has provided an alternative and complementary approach to the development of vaccines against **HIV** in man which is still being pursued. Live attenuated vaccines were initially dismissed as far too hazardous. However, the concept has recently been reexamined in the light of powerful evidence that attenuated SIV induces potent protection against a wide variety of viruses administered by intravenous or **mucosal** routes and even against challenge with viable virus-infected spleen cells. Efforts are now underway to understand the mechanism of this protection and to attempt to reproduce it by less hazardous means. Considerable effort has been devoted to the development of subunit **HIV** vaccines, predominantly based on the **envelope** glycoproteins of the virus. Extensive clinical trials in human volunteers have established that these vaccines are safe and antigenic. However, the immune responses appear to be transient and the antibodies induced do not **neutralize** the primary isolates of **HIV** which are circulating in the population. There are now three possible approaches to an AIDS vaccine which are being actively pursued.

L5 ANSWER 3 OF 22 MEDLINE on STN

96407302. PubMed ID: 8811355. Correlates of protective immunity against **HIV**-1 infection in immunized chimpanzees. Murthy K K; Cobb E K; Rouse S R; Lunceford S M; Johnson D E; Galvan A R. (Department of Virology and Immunology, Southwest Foundation for Biomedical Research, San Antonio, TX 78228-0147, USA.) Immunology letters, **(1996 Jun)** 51 (1-2) 121-4. Ref: 27. Journal code: 7910006. ISSN: 0165-2478. Pub. country: Netherlands. Language: English.

AB Several experimental vaccination strategies have been developed to prevent primary infection with **human immunodeficiency virus** (**HIV**), and as immunotherapeutics for infected individuals. Many of the putative vaccines have been tested in chimpanzees (p. troglodytes) to determine their safety, efficacy, and to delineate immune correlates of protection. To date, approximately 25 candidate vaccines representing active or passive strategies have been evaluated in chimpanzees, and efficacy has been based on protection against primary infection following intravenous or **mucosal** challenge with cell-free or cell-associated virus. Active immunization has been attempted with whole inactivated virus, **envelope** depleted viral preparation, vaccinia vector expressing gp 160 in combination with other viral gene products, and subunit vaccines containing recombinant gp 120 derived from different isolates. Polyclonal and monoclonal antibodies with **neutralizing** activity have been utilized for pre- and post-exposure passive immunization to block primary infection with **HIV**.

L5 ANSWER 4 OF 22 MEDLINE on STN

96264725. PubMed ID: 8683152. **Mucosal** immunity to **HIV**-1: systemic and vaginal antibody responses after intranasal immunization with the **HIV**-1 C4/V3 peptide T1SP10 MN(A). Staats H F; Nichols W G; Palker T J. (Department of Medicine, Center for AIDS Research, Duke University Medical Center, Durham, NC 27710, USA.) Journal of immunology (Baltimore, Md. : 1950), **(1996 Jul 1)** 157 (1) 462-72. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB To optimize **mucosal** immune responses to the **HIV**-1 peptide vaccine candidate T1SP10 MN(A), we intranasally immunized BALB/c and C57BL/6 mice with C4/V3 **HIV**-1 peptide together with the **mucosal** adjuvant cholera toxin (CT). Four doses over a 4-wk period resulted in peak serum anti-peptide IgG titers of > 1:160,000 in BALB/c mice and > 1:520,000 in C57BL/6 mice, and significant levels (>1:30,000) persisted in both strains of mice for longer than 6 mo. Furthermore, intranasal immunization with peptide and CT induced serum IgG reactivity to **HIV**-1 **gp120** and **HIV**-1(MN) **neutralizing** responses. The primary anti-peptide IgG subclass was IgG1, suggesting a predominant Th2-type response. In addition to elevated serum anti-peptide A responses, intranasal

immunization with T1SP10 MN(A) and CT induced both vaginal anti-peptide IgG and **IgA** responses, which persisted for 91 days in both strains of mice. Vaginal anti-**HIV** **IgA** was frequently associated with secretory component, suggesting transepithelial transport of **IgA** into vaginal secretions. Cervical lymph nodes contained the highest relative concentration of anti-T1SP10 MN(A) IgG-producing cells, while the spleen was the next major site of anti-T1SP10 MN(A) IgG-producing cells. Ag-specific proliferative responses were also detected in cervical lymph node and spleen cell populations after intranasal immunization with T1SP10 MN(A) and CT. In addition, intranasal immunization with T1SP10 MN(A) and CT was able to induce anti-**HIV** cell-mediated immunity in vivo as indicated by the induction of delayed-type hypersensitivity. Therefore, intranasal immunization with hybrid **HIV** peptides provides a noninvasive route of immunization that induces both long-lived systemic and **mucosal** Ab responses as well as cell-mediated immunity to **HIV**.

L5 ANSWER 5 OF 22 MEDLINE on STN

96071531. PubMed ID: 7585151. **Neutralization** of **HIV**-1 by secretory **IgA** induced by oral immunization with a new macromolecular multicomponent peptide vaccine candidate. Bukawa H; Sekigawa K; Hamajima K; Fukushima J; Yamada Y; Kiyono H; Okuda K. (Department of Oral and Maxillofacial Surgery, Yokohama City University School of Medicine, Japan.) Nature medicine, **(1995 Jul)** 1 (7) 681-5. Journal code: 9502015. ISSN: 1078-8956. Pub. country: United States. Language: English.

AB Control of pandemic infection of **human immunodeficiency virus** type 1 (**HIV**-1) requires some means of developing **mucosal** immunity against **HIV**-1 because sexual transmission of the virus occurs mainly through the **mucosal** tissues. However, there is no evidence as yet that the secretory immunoglobulin A (**IgA**) antibody induced by immunization with antigens in experimental animals can **neutralize** **HIV**-1. We demonstrate here that oral immunization with a new macromolecular peptide antigen and cholera toxin (CT) induces a high titre (1:2") of gut-associated and secretory **IgA** antibody to **HIV**-1. Using three different **neutralizing** assays, we clearly demonstrate that this secretory **IgA** antibody is able to **neutralize** **HIV**-1IIIB, **HIV**-1SF2 and **HIV**-1MN. Our new approach may prove to be important in the development of a **mucosal** vaccine that will provide protection of **mucosal** surfaces against **HIV**-1.

L5 ANSWER 6 OF 22 MEDLINE on STN

96013760. PubMed ID: 7474077. **Mucosal** model of immunization against **human immunodeficiency virus** type 1 with a chimeric influenza virus. Muster T; Ferko B; Klima A; Purtscher M; Trkola A; Schulz P; Grassauer A; Engelhardt O G; Garcia-Sastre A; Palese P; +. (Institut fur Angewandte Mikrobiologie, Universitat fur Bodenkultur, Vienna, Austria.) Journal of virology, **(1995 Nov)** 69 (11) 6678-86. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Previously, we constructed a chimeric influenza virus that expresses the highly conserved amino acid sequence ELDKWA of **gp41** of **human immunodeficiency virus** type 1 (**HIV**-1). Antisera elicited in mice by infection with this chimeric virus showed **neutralizing** activity against distantly related **HIV**-1 isolates (T. Muster, R. Guinea, A. Trkola, M. Purtscher, A. Klima, F. Steindl, P. Palese, and H. Katinger, J. Virol. 68:4031-4034, 1994). In the present study, we demonstrated that intranasal immunizations with this chimeric virus are also able to induce a humoral immune response at the **mucosal** level. The immunized mice had ELDKWA-specific immunoglobulins A in respiratory, intestinal, and vaginal secretions. Sustained levels of these secretory immunoglobulins A were detectable for more than 1 year after immunization. The results show that influenza virus can be used to efficiently induce secretory antibodies against antigens from foreign pathogens. Since long-lasting **mucosal** immunity in the genital and intestinal tracts might be essential for protective immunity against **HIV**-1, influenza virus appears to be a promising vector for **HIV**-1-derived immunogens.

L5 ANSWER 7 OF 22 MEDLINE on STN

95275458. PubMed ID: 7755912. Safety and immunogenicity of a V3 loop synthetic peptide conjugated to purified protein derivative in **HIV**-seronegative volunteers. Rubinstein A; Goldstein H; Pettoello-Mantovani M; Mizrachi Y; Bloom B R; Furer E; Althaus B; Que J U; Hasler T; Cryz S J. (Albert Einstein College of Medicine, Bronx, New York 10461, USA.) AIDS (London, England), **(1995 Mar)** 9 (3) 243-51. Journal code: 8710219. ISSN: 0269-9370. Pub. country: United States. Language: English.

AB OBJECTIVES: To develop a peptide-based model for a preventive vaccine for **HIV**-1 infection. DESIGN: Phase I trial in **HIV**-1-seronegative volunteers. PARTICIPANTS: Adult healthy subjects **HIV**-1-antibody-seronegative in an enzyme-linked immunosorbent assay, screened for tuberculin [purified protein derivative (PPD)] reactivity with 2 tuberculin units PPD-administered intradermally. INTERVENTIONS:

Submicrogram doses of a PPD conjugate with a peptide of the primary **neutralizing** domain (PND) of **HIV**-1MN (PPD-MN-PND) were administered intradermally to tuberculin skin-test-positive and -negative volunteers. RESULTS: Antibodies to the MN-PND were measured after two immunizations in 10 out of 11 PPD skin-test-positive volunteers. After the fourth immunization high-affinity antibodies were detected, which persisted for over 1 year. High titers of MN-PND-specific immunoglobulin (Ig) G and **IgA** were detected in the serum and saliva of all volunteers tested. Serum antibodies were cross-reactive with PND peptide from some other **HIV**-1 strains but **neutralized** only the **HIV**-1MN prototype. Human leukocyte antigen (HLA)-B7-restricted MN-PND-specific cytotoxic T lymphocytes (CTL) were also detected. CONCLUSIONS: The PPD-MN-PND vaccine at submicrogram doses is safe and immunogenic in PPD skin-test-positive healthy adult volunteers. Long lasting humoral immune responses in the serum and saliva were possibly accompanied by HLA-B7-restricted CTL responses. This is a vaccine prototype that can be rapidly and inexpensively modified to include other peptide epitopes. It is especially suitable for use in a worldwide multibillion Bacillus Calmette-Guerin (BCG)-primed or tuberculosis-exposed population at risk for **HIV**-1 infection.

L5 ANSWER 8 OF 22 MEDLINE on STN

95194704. PubMed ID: 7888199. Immunogenicity of recombinant adenovirus-**human immunodeficiency virus** vaccines in chimpanzees following intranasal administration. Lubeck M D; Natuk R J; Chengalvala M; Chanda P K; Murthy K K; Murthy S; Mizutani S; Lee S G; Wade M S; Bhat B M; +. (Department of Biotechnology and Microbiology, Wyeth-Ayerst Research, Radner, Pennsylvania 19087.) AIDS research and human retroviruses, **(1994 Nov)** 10 (11) 1443-9. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.

AB Recombinant adenovirus (Ad)-**human immunodeficiency virus** (**HIV**) vaccines expressing HIVIIIB **Env** and Gag proteins were evaluated for immunogenicity in chimpanzees following intranasal administration. When Ad7-, Ad4-, and Ad5-vectored vaccines were administered sequentially at 0, 24, and 52 weeks, respectively, to three chimpanzees, the inoculations resulted in limited virus replication in the nasopharynx, but extensive Ad-**HIV** replication occurred in the intestine. High-titered IgG serum antibody responses to **Env** and Gag that were nonneutralizing were induced following booster administration of Ad4-**HIV** recombinant viruses. Following the Ad5-**HIV** booster, low levels of **neutralizing** antibodies as well as V3 loop antibodies were induced in all three chimpanzees that persisted for several months. Administration of a **gp160** subunit vaccine (baculovirus derived) in SAF-m 24 weeks later boosted broadly **neutralizing** serum antibodies that peaked within 1 month of the injection. Two additional subunit boosters 19 and 37 weeks later were progressively less effective at stimulating serum **neutralizing** antibody responses. Substantial local immune responses were induced in nasal, vaginal, and salivary secretions following the third Ad-**HIV** intranasal immunization. These responses were further boosted with the **gp160** subunit vaccine, which also stimulated production of rectal antibodies. The predominant responses in all secretions tested were of the IgG isotype, although some **IgA** responses were also detected. Strong blastogenic responses to **HIV** recombinant **Env** and Gag proteins were induced after each immunization.

L5 ANSWER 9 OF 22 MEDLINE on STN

95107997. PubMed ID: 7809077. Infection of vaginal and colonic epithelial cells by the **human immunodeficiency virus** type 1 is **neutralized** by antibodies raised against conserved epitopes in the **envelope** glycoprotein **gp120**. Furuta Y; Eriksson K; Svennerholm B; Fredman P; Horal P; Jeansson S; Vahlne A; Holmgren J; Czerkinsky C. (Department of Clinical Virology, Goteborg University, Sweden.) Proceedings of the National Academy of Sciences of the United States of America, **(1994 Dec 20)** 91 (26) 12559-63. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB The rectal and genital tract mucosae are considered to be major sites of entry for the **human immunodeficiency virus** (**HIV**) during sexual contact. We now demonstrate that vaginal epithelial cells can be infected by **HIV** type 1 (**HIV**-1) via a mechanism similar to that described for neuroglial cells and, more recently, for colorectal epithelial cells, involving initial interaction of the **HIV**-1 **envelope** glycoprotein **gp120** with a cell-surface glycosphingolipid (sulfated lactosylceramide). A hyperimmune serum against **gp120** was able to **neutralize HIV**-1 infection of vaginal epithelial cells. Site-directed immunization was employed to identify sites on **gp120** recognized by antibodies **neutralizing HIV**-1 infection of vaginal and colonic epithelial cells. Hyperimmune sera were raised in monkeys against a series of 40 overlapping synthetic peptides covering the entire sequence of **HIV**-1 (HTLV-IIIB) **gp120**. Antisera raised against five synthetic peptides, corresponding

to three relatively conserved regions and to the hypervariable region (V3 loop), efficiently **neutralized HIV**-1 infection of human vaginal epithelial cells in vitro. Similar results were obtained with the colonic cells. Hyperimmune sera to all five peptides have been shown earlier to **neutralize HIV**-1 infectivity in CD4+ T cells. These results have obvious implications for the design of **mucosal** subunit vaccines against sexually transmitted **HIV**-1 infections.

L5 ANSWER 10 OF 22 MEDLINE on STN

95078000. PubMed ID: 7986587. Contrasting **IgA** and IgG **neutralization** capacities and responses to **HIV** type 1 **gp120** V3 loop in **HIV**-infected individuals. Kozlowski P A; Chen D; Eldridge J H; Jackson S. (Department of Microbiology, University of Alabama at Birmingham 35294.) AIDS research and human retroviruses, **(1994 Jul)** 10 (7) 813-22. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.

AB Quantitative analysis for **HIV**-1-specific antibodies present in **IgA** and IgG preparations purified from the serum of **HIV**-seropositive individuals indicated that the proportion of **HIV**-specific antibodies present within the IgG isotype was seven times greater than the proportion of **IgA HIV** antibodies present within the **IgA** isotype. Dilution of **IgA HIV**-specific antibodies by nonspecific **IgA** was observed in patients with elevated serum **IgA** concentrations, whereas proportions of IgG **HIV** antibodies rose with increases in concentrations of serum IgG. Although proportions of **IgA HIV** antibodies were not observed to correlate with the CD4 counts of the individuals from whom immunoglobulins were purified, a significant association between the numbers of such cells and proportion of **HIV** antibodies present in the IgG isotype was found. Equivalent amounts of IgG were also more effective than **IgA** at inhibiting **HIV**-1IIIB infection of a susceptible T cell line. This may be due to the presence of higher proportions of IgG antibodies directed toward non-V3 determinants because reactivity against an **HIV**-1IIIB V3 peptide was low and did not differ significantly between these isotopes. **IgA** antibodies reacting against a V3 peptide containing the **HIV** consensus sequence could be detected in the majority of **IgA** samples purified from infected individuals. Proportions of IgG consensus V3-specific antibodies within the purified IgG samples were, however, much higher. The presence of accompanying increases in serum IgG concentration and proportions of IgG **HIV** antibodies, higher proportions of both **HIV**- and consensus V3-specific antibodies within this isotype, and more effective **neutralization** by IgG suggests that an **HIV**-driven response is dominated by B cells committed to production of this immunoglobulin isotype. The observed low proportions of **HIV** antigen-specific **IgA** antibodies with dilution in many individuals by elevations in non-**HIV**-specific **IgA** suggests that **IgA** B cells may be more susceptible to factors that mediate the polyclonal activation believed to be responsible for many of the B cell disorders characteristic of **HIV** infection.

L5 ANSWER 11 OF 22 MEDLINE on STN

95074881. PubMed ID: 7983725. Synthetic multimeric peptides derived from the principal **neutralization** domain (V3 loop) of **human immunodeficiency virus** type 1 (**HIV**-1) **gp120** bind to galactosylceramide and block **HIV**-1 infection in a human CD4-negative **mucosal** epithelial cell line. Yahi N; Sabatier J M; Baghdiguian S; Gonzalez-Scarano F; Fantini J. (CNRS URA 1455, Laboratoire de Biochimie, Faculte de Medecine Nord, Marseille, France.) Journal of virology, **(1995 Jan)** 69 (1) 320-5. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB The glycosphingolipid galactosylceramide (GalCer), which binds **gp120** with high affinity and specificity, is a potential alternative receptor for **human immunodeficiency virus** type 1 (**HIV**-1) in some CD4-negative neural and epithelial human cells, including the human colonic epithelial cell line HT-29. In the present study, we demonstrate that synthetic multibranched peptides derived from the consensus sequence of the **HIV**-1 V3 loop block **HIV**-1 infection in HT-29 cells. The most active peptide was an eight-branched multimer of the motif Gly-Pro-Gly-Arg-Ala-Phe which at a concentration of 1.8 microM induced a 50% inhibition of **HIV**-1 infection in competition experiments. This peptide was not toxic to HT-29 cells, and preincubation with **HIV**-1 did not affect viral infectivity, indicating that the antiviral activity was not due to a nonspecific virucidal effect. Using a high-performance thin-layer chromatography binding assay, we found that multibranched V3 peptides recognized GalCer and inhibited binding of recombinant **gp120** to the glycosphingolipid. In addition, these peptides abolished the binding of an anti-GalCer monoclonal antibody to GalCer on the surface of live HT-29 cells. These data provide additional evidence that the V3 loop is involved in the binding of **gp120** to the GalCer receptor and show that multibranched V3 peptides are potent inhibitors of the GalCer-dependent

pathway of **HIV**-1 infection in CD4-negative **mucosal** epithelial cells.

L5 ANSWER 12 OF 22 MEDLINE on STN
94209687. PubMed ID: 8157978. Serum **IgA**-mediated **neutralization** of **HIV** type 1. Burnett P R; VanCott T C; Polonis V R; Redfield R R; Birx D L. (U.S. Army Dental Research Detachment, Washington, DC 20307.) Journal of immunology (Baltimore, Md. : 1950), **(1994 May 1)** 152 (9) 4642-8. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.
AB The sera of 33 **HIV**-1-infected individuals, previously shown to **neutralize HIV**-1MN in vitro, were screened by ELISA for **IgA** reactivity against rgp120MN and a synthetic V3MN loop peptide. Six were selected for evaluation of the effect of serum **IgA** from infected individuals on the in vitro infection of susceptible target cells by **HIV**-1MN. By using protein G immobilized on Sepharose, we depleted the sera of IgG to a level undetectable by nephelometry and viral **envelope**-specific ELISA. The **IgA** component of the IgG-depleted serum was affinity purified with immobilized jacalin, a lectin that selectively binds the IgA1 fraction of human Ig. IgG-depleted sera and purified IgA1 serum fractions showing **IgA** reactivity against rgp120MN and V3MN by ELISA inhibited the in vitro infection of CEM-ss cells by **HIV**-1MN, but sera depleted of both IgG and IgA1 did not. These data show that, like serum IgG, serum **IgA** from selected **HIV**-1-infected individuals is capable of **neutralizing HIV**-1MN in vitro. The biologic significance of this observation and the identities of serum **IgA**-recognized **HIV**-1 **neutralization** epitopes remain to be determined.

L5 ANSWER 13 OF 22 MEDLINE on STN
93211206. PubMed ID: 8096270. Breast milk and **HIV**-1 transmission. Mok J. (Regional Infectious Diseases Unit, City Hospital, Edinburgh, UK.) Lancet, **(1993 Apr 10)** 341 (8850) 930-1. Journal code: 2985213R. ISSN: 0140-6736.
Report No.: PIP-081605; POP-00221161. Pub. country: ENGLAND: United Kingdom. Language: English.
AB Leukocyte numbers, lactoferrin and **IgA** levels, and lymphocyte mitogenic activity in breast milk fall greatly to almost 0 during the first 2-3 months postpartum, but lactoferrin and **IgA** levels rise during the 3rd-12th month postpartum. Regardless of mother's **HIV**-1 status, breast-fed infants suffer fewer episodes of gastrointestinal and respiratory illnesses than do bottle-fed infants. Breast-fed, **HIV**-1 infected infants experience a longer median incubation period than do bottle-fed infants (19 vs. 9.7 months). The progression to AIDS in breast-fed infants is slower than in bottle-fed infants. The risk of **HIV**-1 transmission from a mother infected after delivery is 29% while it is 14% from a mother infected before delivery, suggesting that antibodies acquired transplacentally or through breast milk protect against **HIV**-1 infection in infants. Breast milk samples from 15 **HIV**-1 infected mothers reveal IgG and **IgA** antibodies against **envelope** glycoproteins and **IgA** antibodies against core antigens. A human milk factor blocks binding of **HIV**-1 to the CD4 receptor. A report in this issue of The Lancet shows **HIV**-1 specific IgM and **IgA** in 15-day postpartum breast milk, regardless of mother's immune status. There is a linear relationship between the persistence of these antibodies and the absence of **HIV**-1 infection in the infants. The authors believe **neutralizing** or cytotoxic activity protects infants against **HIV**-1 infection. More needs to be learned about **mucosal** transmission. If a cell-associated virus is responsible for **HIV**-1 infection, then the colostrum would be more infectious. Perhaps **HIV**-1 transmission could be reduced if mothers express and discard the colostrum and the early milk. This would be important to know, especially for women in developing countries. Further research is needed to learn how and when perinatal **HIV**-1 transmission occurs. In the interim, in areas where a safe alternative to breast milk exists, **HIV**-1 infected mothers should not breast feed.

L5 ANSWER 14 OF 22 MEDLINE on STN
93163242. PubMed ID: 1287035. Serum antibodies to **HIV**-1 in recombinant vaccinia virus recipients boosted with purified recombinant **gp160**. NIAID AIDS Vaccine Clinical Trials Network. Montefiori D C; Graham B S; Kliks S; Wright P F. (Department of Pathology, Vanderbilt University Medical School, Nashville, Tennessee 37232.) Journal of clinical immunology, **(1992 Nov)** 12 (6) 429-39. Journal code: 8102137. ISSN: 0271-9142. Pub. country: United States. Language: English.
AB Serum antibody responses were studied in detail in four vaccinia-naive volunteers in a phase I trial evaluating primary vaccination with a recombinant vaccinia virus expressing the **HIV**-1 **gp160 envelope** glycoprotein (HIVAC-1e, Oncogen/Bristol-Myers Squibb), followed by booster immunization with baculovirus-derived rgp160 (VaxSyn, MicroGeneSys). Prior to boosting, low-titer Fc receptor (FcR)-mediated, antibody-dependent enhancing (ADE) activity was detected in two of four

volunteers but no IgM, IgG, **IgA**, **neutralizing** activity, or complement-mediated ADE activity was detected. Two weeks after boosting, all four volunteers developed **HIV**-1-specific IgG with titers of 1:160 to 1:640 by immunofluorescence assay. IgG1 was present in sera from each individual, while IgG2 and IgG3 were present in sera from two individuals, and IgG4 was present in serum from one individual. IgM and **IgA** were undetectable in all sera. Only one volunteer had IgG to the heterologous **HIV**-1 isolates, RF, MN, and SF2, after boosting. Serum from this volunteer **neutralized** the vaccine strain, LAV/IIIB, but not the heterologous strains, RF, MN, and SF2. Antibodies from the remaining volunteers had no **neutralizing** activity. The **neutralizing** serum had a positive reaction in a peptide-based ELISA utilizing a peptide corresponding to the principal **neutralizing** domain of the third hypervariable region (i.e., V3 loop) of the **envelope** glycoprotein. **Neutralizing** activity was partially removed by adsorption to this peptide, suggesting that it contained a type-specific **neutralizing** vaccine epitope. A low titer (1:40 to 1:80) of complement-mediated ADE activity to **HIV**-1 IIIB was present in sera from three vaccinees after boosting. FcR-ADE activity for **HIV**-1 SF2 and SF-128A were present in sera from two of these three vaccinees. None of the volunteers developed antisyncytial antibodies. These results indicate that inoculation with recombinant vaccinia followed by rgp160 boosting is the most effective strategy to date for inducing serum antibodies to the **envelope** glycoproteins of **HIV**-1, but further study is needed to optimize the functionality and cross-reactivity of these responses.

L5 ANSWER 15 OF 22 MEDLINE on STN

92356096. PubMed ID: 1645152. Vaginal immunization of rats with a synthetic peptide from **human immunodeficiency virus envelope** glycoprotein. O'Hagan D T; Rafferty D; McKeating J A; Illum L. (Department of Pharmaceutical Sciences, University of Nottingham, University Park, U.K.) Journal of general virology, **(1992 Aug)** 73 (Pt 8) 2141-5. Journal code: 0077340. ISSN: 0022-1317. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Local secretory immunity in the vagina may confer a degree of protection against heterosexual transmission of **human immunodeficiency virus** (**HIV**). Since the vagina has been shown to respond to local immunization, we have undertaken intravaginal immunization of rats with a 20-mer peptide (amino acid residues 102 to 121) of the **HIV**-1 **envelope** glycoprotein (**gp120**). The peptide was administered in combination with an 'absorption enhancer', lysophosphatidyl glycerol (LPG), which has previously been shown to promote the absorption of intravaginally administered peptides, while exerting only mild effects on epithelial membrane integrity. Intravaginal immunization with LPG and the peptide induced serum and vaginal wash **IgA** and IgG antibody responses which were enhanced in comparison to those after immunization with the peptide alone. Serum antibodies induced by both subcutaneous and intravaginal immunization were able to recognize recombinant **HIV**-1 **gp120**. However, the rat antiserum displayed no **neutralizing** activity against the virus. These results demonstrate that LPG is an effective immunological adjuvant for intravaginally administered peptide antigens. An alternative absorption enhancer, bestatin (BES), was not effective as an immunological adjuvant when administered intravaginally and blocked the adjuvant activity of LPG when BES and LPG were used in combination.

L5 ANSWER 16 OF 22 MEDLINE on STN

92101607. PubMed ID: 1759500. SIV vaccines: current status. The role of the SIV-macaque model in AIDS research. Gardner M. (Department of Pathology, School of Medicine, University of California, Davis 95616.) Vaccine, **(1991 Nov)** 9 (11) 787-91. Ref: 41. Journal code: 8406899. ISSN: 0264-410X. Pub. country: ENGLAND: United Kingdom. Language: English.

AB SIV vaccines made of inactivated whole virus, modified live virus and native and recombinant **envelope** antigens have protected macaques against experimental infection with low doses of cell-free SIV given systemically. The few vaccinated monkeys that do become infected have tended to live longer than the infected controls. Protection against cell-associated virus has not as yet been tested. The recombinant **envelope** vaccines now on test have generally not been as effective as the whole virus vaccines. Post-infectious immunotherapy with SIV vaccines has been ineffective. The same whole virus and modified live virus vaccines that protect against systemic infection fail to protect against genital **mucosal** challenge with cell-free virus. Since sexual transmission is the major route of **HIV** spread on a global scale, a major effort is now required to develop vaccines in this animal model that induce genital **mucosal** as well as systemic immunity against infection with both cell-free and cell-associated SIV.

L5 ANSWER 17 OF 22 MEDLINE on STN

92087468. PubMed ID: 1370128. Mechanism of **HIV** spread from lymphocytes

to epithelia. Phillips D M; Bourinbaiar A S. (Population Council, Center for Biomedical Research, New York, New York 10021.) Virology, **(1992 Jan)** 186 (1) 261-73. Journal code: 0110674. ISSN: 0042-6822. Pub. country: United States. Language: English.

AB Contact of **human immunodeficiency virus** (**HIV**)-infected MOLT-4 lymphocytes with epithelial cells derived from small intestine (I407; Intestine 407) resulted in a rapid polar budding of viral particles into an enclosed space formed by interdigitating microvilli of the contacting cells. Electron microscopy showed that released **HIV** was taken up into the **mucosal** cell via three independent mechanisms: (1) phagocytosis, (2) coated pits, and (3) direct fusion. Morphological evidence suggests that internalized **HIV** may escape into the cytoplasm of the target cell by uncoating at the endosomal membrane. Based on CD4 antibody binding and CD4 antibody blocking experiments, **HIV** entry does not appear to be mediated by a viral CD4 receptor. Productivity of I407 infection was confirmed by virus isolation from cocultured MT-4 lymphocytic cells, reverse transcriptase assay, p24 antigen ELISA, in situ **HIV** mRNA hybridization, and Southern dot blot analysis. Contrary to infection with free virus, the cell-to-cell infection was not blocked by anti-**gp120** or antiviral serum from **HIV**-positive individuals. It appears that **HIV** transmission within the confined space between contacting cells enables **HIV** to evade immune protection provided by **neutralizing** antibodies. Our results reveal a mechanism of **HIV** infection of epithelial cells which is triggered by cell-cell contact. Furthermore, these observations offer an insight into the cellular sequence of events which may take place during sexual transmission of **HIV** across an intact epithelial barrier.

L5 ANSWER 18 OF 22 MEDLINE on STN

92060968. PubMed ID: 1659310. Simian and feline immunodeficiency viruses: animal lentivirus models for evaluation of AIDS vaccines and antiviral agents. Gardner M B. (Department of Medical Pathology, University of California, Davis 95616.) Antiviral research, **(1991 May)** 15 (4) 267-86. Ref: 82. Journal code: 8109699. ISSN: 0166-3542. Pub. country: Netherlands. Language: English.

AB Infection of captive macaques with simian immunodeficiency virus (SIV) and domestic cats with feline immunodeficiency virus (FIV), both discovered in the last five years, represent excellent animal models for infection of humans with the **human immunodeficiency virus** (**HIV**). Protection against challenge infection and protection against development of simian and feline acquired immunodeficiency syndrome has been achieved in each model by use of inactivated whole virus or virus-cell vaccines. A recombinant SIV **envelope** peptide vaccine has also proved efficacious. These vaccines have protected against 10-100 animal infectious doses of the homologous cell-free virus given systemically, and, in the simian model, apparently show cross protection against a heterologous strain of SIV. Protected animals appear free of any latent infection although late breakthroughs of infection in a few animals imply that not all vaccinated animals are completely protected. The mechanism of protection in the simian model apparently involves **envelope** antibody but the role of **neutralizing** antibody remains unclear. Questions remaining to be answered in both SIV and FIV models are: (1) the duration of immunity, (2) the extent of protection against heterologous strains and **mucosal** infection, (3) protection against infection with cell-associated virus and (4) the role, if any, of cellular immunity in vaccine protection. Initial attempts at post-infection immunotherapy with SIV vaccines have not yet been successful. The inactivated whole SIV and FIV vaccines offer a promising start and provide hope that a prophylactic AIDS vaccine will be developed. Use of these animal models for antiviral therapy is just now getting underway. Both models should prove especially useful for studies of prophylaxis and therapy, especially during the early stages of infection and for investigations on drug pharmacokinetics or toxicity that can not be done as well in **HIV**-infected humans. The animals will also be ideal for testing the pathogenicity of drug-induced mutant forms of SIV and FIV. For these purposes it will be necessary to create self-sustaining specific pathogen-free macaque and cat breeding colonies and provide increased housing facilities for infected animals. The future of AIDS research is crucially dependent on the long term availability of these animal models.

L5 ANSWER 19 OF 22 MEDLINE on STN

91370198. PubMed ID: 1892992. The interaction of salivary secretions with the human complement system--a model for the study of host defense systems on inflamed **mucosal** surfaces. Boackle R J. (Department of Microbiology and Immunology, College of Dental Medicine, Medical University of South Carolina, Charleston.) Critical reviews in oral biology and medicine : an official publication of the American Association of Oral Biologists, **(1991)** 2 (3) 355-67. Ref: 82. Journal code: 9009999. ISSN: 1045-4411. Pub. country: United States. Language: English.

AB When complement first contacts salivary secretions, as when gingival

crevicular fluid first meets saliva at the gingival margin, complement function is enhanced. The immediate potentiation of the complement system at equal volume ratios of serum to saliva is due to several factors, including the lower ionic strength of saliva when compared with serum and the presence of certain salivary glyproteins such as the nonimmunoglobulin agglutinins that appear to simultaneously activate C1 and affect (sequester) certain complement control proteins, such as Factor H. This initial potentiation of the complement cascade by saliva may aid in defending the area immediately above the gingival crevice from oral microbiota that are being coated with a combination of serous exudate components and salivary components. As serum becomes much more diluted with saliva (i.e., crevicular fluid moves away from the supragingival area), the acidic proline-rich salivary proteins (APRP) begin to disrupt the unbound C1q-C1r2-C1s2 macromolecular complexes. Thus, the APRP along with other C1 fixing substances in saliva appear to restrict complement function, but only when the ratios of saliva to serum exceed 250:1. Since certain salivary glycoproteins bind to viruses, the potentiation of the complement system by saliva may also play a role in **neutralizing** certain viral infections on **mucosal** surfaces where tissue transudates containing complement begin to contact **mucosal** secretions such as saliva. Again, the ratio of serous fluid to **mucosal** secretion appears to be an important factor. This article also discusses some of our preliminary data and speculations concerning the binding of the self-associating high-molecular-weight nonimmunoglobulin salivary agglutinins (NIA) with the **envelope** of the **human immunodeficiency virus** (**HIV**) and the possible cooperative role of C1q and fibronectin in aiding **neutralization** of **HIV** infectivity.

L5 ANSWER 20 OF 22 MEDLINE on STN

91293470. PubMed ID: 2065890. Mother-to-child transmission of **human immunodeficiency virus**. Rossi P; Moschese V. (Department of Immunology, Karolinska Institute, Stockholm, Sweden.) FASEB journal : official publication of the Federation of American Societies for Experimental Biology, **(1991 Jul)** 5 (10) 2419-26. Ref: 66. Journal code: 8804484. ISSN: 0892-6638. Pub. country: United States. Language: English.

AB Transmission of **HIV** virus from an infected mother to her offspring is becoming the leading cause of spreading in the pediatric population. This is particularly burdensome in the pattern II countries where **HIV** infection has reached epidemic proportions and infection rates affect more women of childbearing age than men. During the last few years considerable effort has been directed at defining the optimal methods for identifying infants of **HIV**-infected mothers who will themselves prove to be infected because conventional serological assessment is impaired due to placental transfer of maternal IgG. At present, detection of specific **IgA** to **HIV** proteins, evaluation of autochthonous antibody production in vitro from infants' lymphocytes, and gene amplification of **HIV** DNA/RNA by polymerase chain reaction are the most promising procedures for early diagnosis within the first 6 months of life. Nevertheless all these techniques are cumbersome when evaluating specimens from the newborn child. Many studies have been performed to identify those maternal factors affecting the risk of vertical transmission. So far, none of them has shown real prognostic value. However, evaluation of maternal antibody response to functional epitopes of **HIV envelope** proteins such as the principal **neutralizing** domain, in some epidemiological settings, seems to correlate to a reduced rate of mother-to-child transmission.

L5 ANSWER 21 OF 22 MEDLINE on STN

91220713. PubMed ID: 1708933. Homotypic antibody responses to fresh clinical isolates of **human immunodeficiency virus**. Montefiori D C; Zhou I Y; Barnes B; Lake D; Hersh E M; Masuho Y; Lefkowitz L B Jr. (Department of Pathology, Vanderbilt University Medical School, Nashville, Tennessee 37232.) Virology, **(1991 Jun)** 182 (2) 635-43. Journal code: 0110674. ISSN: 0042-6822. Pub. country: United States. Language: English.

AB **Human immunodeficiency virus** type 1 (**HIV**-1) exhibits extensive genomic and antigenic diversity, which is thought to contribute to the failure of the host's immune response to control infection and prevent clinical progression. Part of this failure may be due to utilization by the virus of antigenic variation as a means to escape protective immune responses. Antibody-escape variants of **HIV**-1 were studied here using fresh clinical isolates and autologous plasmas. **HIV**-1 was isolated from the plasma of seven people who were all seropositive for at least 2 years, and symptomatic sometime during that period. Isolated viruses were confirmed as **HIV**-1 by the presence of reverse transcriptase activity in infected culture supernatants, and by positive immunofluorescence using human monoclonal antibody to **HIV**-1 core protein. Plasma from these people were positive by Western immunoblot (DuPont) for most major **HIV**-1 (strain IIIB) antigens. These plasmas **neutralized** three laboratory strains of **HIV**-1 (i.e., IIIB, RF, and MN) but did not **neutralize** the homotypic strain in five cases, and had greatly reduced **neutralizing**

titers against the homotypic strain in two cases. Homotypic **neutralizing** antibodies were absent in autologous plasma obtained 3 months later. When antibody titers were measured by fixed-cell indirect immunofluorescence assays (IFAs), high titers of IgG (1:6400 to 1:25,600) were detected against **HIV**-1 IIIB, while low titers of only 1:20 to 1:160 were detected against homotypic viral antigens at the time of virus isolation, and remained low 12 and 16 weeks later. No class **IgA**, IgD, IgE, or IgM antibodies to homotypic viral antigens, as possible IgG-blocking antibodies, were detected by fixed-cell IFAs. Cross-reactions with heterologous donor's plasmas were observed in some cases, and in these cases the cross-reactions were unidirectional. Live-cell IFAs detected IgG in patient's plasma to **HIV**-1 IIIB-infected cells but not to cells infected with homotypic isolates. These results suggest that it is common for **neutralization**-resistant **HIV**-1 variants to appear during the course of infection, and that all or most antigens of these variants are capable of escaping antibody recognition.

L5 ANSWER 22 OF 22 MEDLINE on STN

88209353. PubMed ID: 3163253. Isotypic restriction of the antibody response to **human immunodeficiency virus**. Khalife J; Guy B; Capron M; Kieny M P; Ameisen J C; Montagnier L; Lecocq J P; Capron A. (Centre d'Immunologie et de Biologie Parasitaire, Institut Pasteur, Lille, France.) AIDS research and human retroviruses, **(1988 Feb)** 4 (1) 3-9. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.

AB **HIV**-infected individuals progress toward AIDS despite the early elicitation of a specific immune response. Analysis of the isotypic distribution of **HIV**-specific antibodies appears of special interest for two reasons: first, isotypic diversity is partly under the control of antigen-specific T-helper cells, the very cells infected by **HIV**; second, isotype determines antibody functions, effector (**neutralization**, antibody-dependent complement, or cell-mediated cytotoxicity) as well as blocking functions. We have investigated by Western blot analysis the isotypic profile of the antibody response to **HIV** structural proteins (**env**, gag, pol) and to the nonstructural protein F (3' orf), which is absent from the virion and might primarily target infected cells. In 115 asymptomatic individuals, infected by sexual contact (homosexual men) or intravenously (hemophiliacs), the response to gag-products was polyisotypic, including IgM, IgG1, IgG3 and **IgA**; the response to F was more restricted (IgM, IgG1, **IgA**) and the response to **env** strikingly restricted to the IgG1 isotype, suggesting different regulatory mechanisms in the B-cell response to these proteins. The isotypic distribution was also influenced by the route of infection, IgG4 and IgE (gag-specific) being exclusively elicited in the hemophiliac group. Finally, observations of potential diagnostic interest were made in a limited number of at-risk individuals; these included the presence of gag- and pol-specific IgM or **IgA** in the absence of any **HIV**-specific IgG isotypes; and the presence of gag- and F-specific antibodies in the absence of **env**-specific antibodies, suggesting the early occurrence of both isotypic and antigenic selection mechanisms during the course of **HIV** infection.

=> file uspatful

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	37.82	38.24

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FILE COVERS 1971 TO PATENT PUBLICATION DATE: 18 Aug 2005 (20050818/PD)
FILE LAST UPDATED: 18 Aug 2005 (20050818/ED)
HIGHEST GRANTED PATENT NUMBER: US6931661
HIGHEST APPLICATION PUBLICATION NUMBER: US2005183181
CA INDEXING IS CURRENT THROUGH 18 Aug 2005 (20050818/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 18 Aug 2005 (20050818/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Jun 2005
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Jun 2005

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>>> publications, starting in 2001, for the inventions covered in <<<
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>>> publication date for all the US publications for an invention <<<
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>>>  /PK, etc.                                                        <<<

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>>>  classifications, or claims, that may potentially change from     <<<
>>>  the earliest to the latest publication.                          <<<

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substance identification.

=> d his

     (FILE 'HOME' ENTERED AT 11:40:40 ON 22 AUG 2005)

     FILE 'MEDLINE' ENTERED AT 11:41:54 ON 22 AUG 2005
L1        155517 S (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L2          1953 S L1 AND (MUCOSAL OR IGA)
L3           420 S L2 AND (ENV? OR GP160 OR GP120 OR GP41)
L4            99 S L3 AND PY<1997
L5            22 S L4 AND NEUTRALIZ?

     FILE 'USPATFULL' ENTERED AT 11:59:54 ON 22 AUG 2005

=> s (HIV or human immunodeficiency virus)
          38639 HIV
         458617 HUMAN
          22079 IMMUNODEFICIENCY
          90756 VIRUS
          15777 HUMAN IMMUNODEFICIENCY VIRUS
                  (HUMAN(W)IMMUNODEFICIENCY(W)VIRUS)
L6        40702 (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)

=> s l6 and (mucosal or IgA)
          18618 MUCOSAL
          14814 IGA
L7        10049 L6 AND (MUCOSAL OR IGA)

=> s l7 and (gp160 or gp120 or gp41)
           1450 GP160
           4170 GP120
           2191 GP41
L8         1708 L7 AND (GP160 OR GP120 OR GP41)

=> s l8 and (mucosal/clm)
           1842 MUCOSAL/CLM
L9          131 L8 AND (MUCOSAL/CLM)

=> s l9 and ay<1997
        2436799 AY<1997
L10          22 L9 AND AY<1997

=> d l10,cbib,1-22

L10  ANSWER 1 OF 22  USPATFULL on STN
2003:268206 Methods for inducing mucosal immune responses.
    Mitchell, William M., Nashville, TN, United States
    Vanderbilt University, Nashville, TN, United States (U.S. corporation)
    US 6630455 B1 20031007
    APPLICATION: US 1995-372429  19950113 (8)                        <--
    DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L10  ANSWER 2 OF 22  USPATFULL on STN
2003:95819 Non-infectious, immunogenic, human immunodeficiency virus-like
    particles devoid of long terminal repeats and a functional pol coding
    region.
    Rovinski, Benjamin, Thornhill, CANADA
    Cao, Shi-Xian, Etobicoke, CANADA
    Yao, Fei-Long, North York, CANADA
    Persson, Roy, North York, CANADA
    Klein, Michel H., Willowdale, CANADA
    Aventis Pasteur Limited, Toronto, CANADA (non-U.S. corporation)
    US 6544527 B1 20030408
    APPLICATION: US 1996-680525  19960709 (8)                        <--
    DOCUMENT TYPE: Utility; GRANTED.
```

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L10 ANSWER 3 OF 22 USPATFULL on STN
2002:34422 Methods of inducing **mucosal** immunity.
Weiner, David B., Merion, PA, United States
Wang, Bin, Havertown, PA, United States
Ugen, Kenneth E., Philadelphia, PA, United States
The Trustees of the University of Pennsylvania, Philadelphia, PA, United States (U.S. corporation)
US 6348449 B1 20020219
APPLICATION: US 1994-357398 19941216 (8) <--
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L10 ANSWER 4 OF 22 USPATFULL on STN
2001:119048 IMMUNOGENIC CONSTRUCT, PROCESS FOR ITS PREPARATION AND USE AS A VACCINE.
MANNHALTER, JOSEF W., VIENNA, Euratom
LEIBL, HEINZ, VIENNA, Euratom
EIBL, MARTHA, VIENNA, Euratom
US 2001009669 A1 20010726
APPLICATION: US 1997-973397 A1 19971212 (8) <--
WO 1996-EP2098 19960515 None PCT 102(e) date <--
PRIORITY: DE 1995-19521705 19950614
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L10 ANSWER 5 OF 22 USPATFULL on STN
2000:97977 **Mucosal** administration of substances to mammals.
Betbeder, Didier, Aucamville, France
Etienne, Alain, Toulouse, France
de Miguel, Ignacio, Toulouse, France
Kravtzoff, Roger, Fourquevaux, France
Major, Michel, Toulouse, France
Biovector Therapeutics, S.A., Labege Cedex, France (non-U.S. corporation)
US 6096291 20000801
APPLICATION: US 1996-774920 19961227 (8) <--
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L10 ANSWER 6 OF 22 USPATFULL on STN
2000:80416 **Human immunodeficiency virus** type 1 nucleic acids devoid of long terminal repeats capable of encoding for non-infectious, immunogenic, retrovirus-like particles.
Rovinski, Benjamin, Thornhill, Canada
Cao, Shi-Xian, Etobicoke, Canada
Yao, Fei-Long, North York, Canada
Persson, Roy, North York, Canada
Klein, Michel H., Willowdale, Canada
Connaught Laboratories Limited, Toronto, Canada (non-U.S. corporation)
US 6080408 20000627
APPLICATION: US 1995-482810 19950607 (8) <--
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L10 ANSWER 7 OF 22 USPATFULL on STN
1999:145984 Oral or intranasal vaccines using hydrophobic complexes having proteosomes and lipopolysaccharides.
Lowell, George H., 6303 Western Run Dr., Baltimore, MD, United States 21215
US 5985284 19991116
APPLICATION: US 1996-677302 19960709 (8) <--
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L10 ANSWER 8 OF 22 USPATFULL on STN
1999:113630 Non-infectious, replication-defective, self-assembling **HIV**-1 viral particles containing antigenic markers in the gag coding region.
Rovinski, Benjamin, Thornhill, Canada
Cao, Shi-Xian, Etobicoke, Canada
Yao, Fei-Long, North York, Canada
Persson, Roy, North York, Canada
Klein, Michel H., Willowdale, Canada
Connaught Laboratories Limited, North York, Canada (non-U.S. corporation)
US 5955342 19990921
APPLICATION: US 1994-290105 19940815 (8) <--
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L10 ANSWER 9 OF 22 USPATFULL on STN
1999:109976 Tandem synthetic **HIV**-1 peptides.
Sia, Charles D. Y., Thornhill, Canada
Chong, Pele, Richmond Hill, Canada
Klein, Michel H., Willowdale, Canada
Connaught Laboratories Limited, North York, Canada (non-U.S. corporation)
US 5951986 19990914
APPLICATION: US 1995-467881 19950606 (8) <--
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L10 ANSWER 10 OF 22 USPATFULL on STN
1999:40590 Nucleic acid molecules encoding non-infectious, non-replicating, **HIV** retrovirus-like particles containing heterologous antigenic anchor sequences.
Rovinski, Benjamin, Thornhill, Canada
Cao, Shi-Xian, Etobicoke, Canada
Yao, Fei-Long, North York, Canada
Persson, Roy, North York, Canada
Klein, Michel H., Willowdale, Canada
Connaught Laboratories Limited, Toronto, Canada (non-U.S. corporation)
US 5889176 19990330
APPLICATION: US 1996-761209 19961206 (8) <--
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L10 ANSWER 11 OF 22 USPATFULL on STN
1999:30609 Genetically engineered **human immunodeficiency virus**-like particles with modified chimeric envelope glycoproteins containing influenza virus transmembrane spanning domains.
Rovinski, Benjamin, Thornhill, Canada
Cao, Shi-Xian, Etobicoke, Canada
Yao, Fei-Long, North York, Canada
Persson, Roy, North York, Canada
Klein, Michel H., Willowdale, Canada
Connaught Laboratories Limited, North York, Canada (non-U.S. corporation)
US 5879925 19990309
APPLICATION: US 1996-761828 19961206 (8) <--
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L10 ANSWER 12 OF 22 USPATFULL on STN
1999:27618 Method for introducing and expressing genes in animal cells and live invasive bacterial vectors for use in the same.
Powell, Robert J., Baltimore, MD, United States
Lewis, George K., Baltimore, MD, United States
Hone, David M., Ellicott City, MD, United States
University of Maryland at Baltimore, Baltimore, MD, United States (U.S. corporation)
US 5877159 19990302
APPLICATION: US 1995-433790 19950503 (8) <--
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L10 ANSWER 13 OF 22 USPATFULL on STN
1999:21889 Reduction of false positives in oral-fluid based immunoassays.
Thieme, Thomas, Independence, OR, United States
Klimkow, Nanette, Beaverton, OR, United States
Epitope, Inc., Beaverton, OR, United States (U.S. corporation)
US 5871905 19990216
APPLICATION: US 1996-707446 19960904 (8) <--
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L10 ANSWER 14 OF 22 USPATFULL on STN
1999:15678 Nucleic acids encoding for non-infectious, replication-defective, self-assembling **HIV**-1 viral particles containing antigenic markers in the gag coding region.
Rovinski, Benjamin, Thornhill, Canada
Cao, Shi-Xian, Etobicoke, Canada
Yao, Fei-Long, North York, Canada
Persson, Roy, North York, Canada
Klein, Michel H., Willowdale, Canada
Connaught Laboratories Limited, North York, Canada (non-U.S. corporation)
US 5866320 19990202
APPLICATION: US 1995-470419 19950606 (8) <--
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L10 ANSWER 15 OF 22 USPATFULL on STN
1998:127915 Vaccine compositions and method for induction of **mucosal** immune response via systemic vaccination.
Daynes, Raymond A., Park City, UT, United States
Araneo, Barbara A., Salt Lake City, UT, United States
University of Utah Research Foundation, Salt Lake City, UT, United States (U.S. corporation)
US 5824313 19981020
APPLICATION: US 1995-480567 19950607 (8) <--
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L10 ANSWER 16 OF 22 USPATFULL on STN
1998:88827 Uses of aloe products in the treatment of chronic respiratory diseases.
Carpenter, Robert H., Bastrop, TX, United States
McDaniel, Harley R., Dallas, TX, United States
McAnalley, Bill H., Grand Prairie, TX, United States
Carrington Laboratories, Inc., Irving, TX, United States (U.S. corporation)
US 5786342 19980728
APPLICATION: US 1995-462821 19950605 (8) <--
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L10 ANSWER 17 OF 22 USPATFULL on STN
1998:64760 Vaccines against intracellular pathogens using antigens encapsulated within biodegradble-biocompatible microspheres.
Burnett, Paul R., Silver Spring, MD, United States
Van Hamont, John E., Ft. Meade, MD, United States
Reid, Robert H., Kensington, MD, United States
Setterstrom, Jean A., Alpharetta, GA, United States
Van Cott, Thomas C., Brookeville, MD, United States
Birx, Debrah L., Potomac, MD, United States
The United States of America as represented by the Secretary of the Army, Washington, DC, United States (U.S. government)
US 5762965 19980609
APPLICATION: US 1996-598874 19960209 (8) <--
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L10 ANSWER 18 OF 22 USPATFULL on STN
1998:33575 Protection from viral infection via colonization of **mucosal** membranes with genetically modified bacteria.
Lee, Peter Poon-Hang, 1130 Welch Rd., Apt. 313, Palo Alto, CA, United States 94304
US 5733540 19980331
APPLICATION: US 1995-401070 19950308 (8) <--
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L10 ANSWER 19 OF 22 USPATFULL on STN
1998:14497 Solid fat nanoemulsions as vaccine delivery vehicles.
Anselem, Shimon, Rehovot, Israel
Lowell, George H., Baltimore, MD, United States
Aviv, Haim, Rehovot, Israel
Friedman, Doron, Carmei Yosef, Israel
Pharmos Corporation, New York, NY, United States (U.S. corporation)The United States of America as represented by the Secretary of the Army, Washington, DC, United States (U.S. government)
US 5716637 19980210
WO 9426255 19941124
APPLICATION: US 1995-553350 19951116 (8) <--
WO 1994-US5589 19940518 19951116 PCT 371 date 19951116 PCT 102(e) date<--
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L10 ANSWER 20 OF 22 USPATFULL on STN
97:99027 Immunological tolerance-inducing agent.
Holmgren, Jan, Vastra Frolunda, Sweden
Czerkinsky, Cecil, Goteborg, Sweden
Duotol AB, Vastra Frolunda, Sweden (non-U.S. corporation)
US 5681571 19971028
APPLICATION: US 1994-184458 19940119 (8) <--
PRIORITY: SE 1993-3301 19931008
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L10 ANSWER 21 OF 22 USPATFULL on STN
97:93891 Enterically administered recombinant poxvirus vaccines.

Small, Jr., Parker A., Gainesville, FL, United States
Bender, Bradley Stephen, Gainesville, FL, United States
Meitin, Catherine Ann, Lake Oswego, OR, United States
Moss, Bernard, Bethesda, MD, United States
University of Florida, Gainesville, FL, United States (U.S. corporation)
US 5676950 19971014
APPLICATION: US 1995-485229 19950607 (8) <--
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L10 ANSWER 22 OF 22 USPATFULL on STN
96:43382 Vaccine compositions and method for induction of **mucosal** immune response via systemic vaccination.
Daynes, Raymond A., Park City, UT, United States
Araneo, Barbara A., Salt Lake City, UT, United States
University of Utah Research Foundation, Salt Lake City, UT, United States (U.S. corporation)
US 5518725 19960521
APPLICATION: US 1993-123844 19930909 (8) <--
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> d l10,cbib,clm,1-22

L10 ANSWER 1 OF 22 USPATFULL on STN
2003:268206 Methods for inducing **mucosal** immune responses.
Mitchell, William M., Nashville, TN, United States
Vanderbilt University, Nashville, TN, United States (U.S. corporation)
US 6630455 B1 20031007
APPLICATION: US 1995-372429 19950113 (8) <--
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A method of inducing a **mucosal** immune response to antigen in a mammal, comprising administering to the mucosa of said mammal antigen-encoding DNA, operably linked to a promoter for expression of said antigen and complexed to a transfection-facilitating lipospermine or lipospermidine, in an amount effective to induce a **mucosal** immune response to expressed antigen.

2. The method of claim 1, wherein the **mucosal** administration is nasal.

3. The method of claim 1, wherein the **mucosal** administration is oral.

4. The method of claim 1, wherein the **mucosal** administration is rectal.

5. The method of claim 1, wherein the **mucosal** administration is vaginal.

6. The method of claim 1, wherein the lipospermine is dioctadecylamidboglycylspermine.

7. The method of claim 1, wherein the DNA encodes an envelope antigen or envelope-associated antigen.

L10 ANSWER 2 OF 22 USPATFULL on STN
2003:95819 Non-infectious, immunogenic, **human immunodeficiency virus**-like particles devoid of long terminal repeats and a functional pol coding region.
Rovinski, Benjamin, Thornhill, CANADA
Cao, Shi-Xian, Etobicoke, CANADA
Yao, Fei-Long, North York, CANADA
Persson, Roy, North York, CANADA
Klein, Michel H., Willowdale, CANADA
Aventis Pasteur Limited, Toronto, CANADA (non-U.S. corporation)
US 6544527 B1 20030408
APPLICATION: US 1996-680525 19960709 (8) <--
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A non-infectious, immunogenic, non-replicating **HIV** retrovirus-like particle comprising, in an assembly, gag, pol and env gene products of **HIV**, wherein said particle is encoded by a modified **HIV** retroviral genome deficient in long terminal repeats (LTRs) and containing gag, pol and env in their native genomic arrangement and wherein modifications have been made to the gag and pol gene products, said modification to said gag product comprising replacement of at least one amino acid residue in the first Cys-His box only of the gag gene product defined by

amino acids Cys^{392} to Cys^{395}, wherein the numbering scheme is based upon isolate **HIV-**1_{LAI}, or the corresponding region of other **HIV**-1 isolates, wherein said replacement results in the abrogation of viral genomic RNA packaging functions; said modification to said pol gene products being one selected from the group consisting of: (a) a single deletion of the pol gene product between amino acids Pro^{168} and Leu^{727}, wherein the numbering scheme is based upon isolate **HIV-**1_{LAI}, or the corresponding region of other **HIV**-1 isolates, wherein said deletion eliminates reverse transcriptase activity and RNase H activity; (b) a single deletion of the pol gene product between amino acids Phe^{728} and Asp^{1016}, wherein the numbering scheme is based upon isolate **HIV-**1_{LAI}, or the corresponding region of other **HIV**-1 isolates, wherein said deletion eliminates integrase activity; and (c) a single deletion of the pol gene product between amino acids Pro^{192} and Trp^{835}, wherein the numbering scheme is based upon isolate **HIV-**1_{LAI}, or the corresponding region of other **HIV**-1 isolates, wherein said deletion eliminates reverse transcriptase, integrase and RNase H activities.

2. An immunogenic composition capable of eliciting a retroviral specific immune response, comprising the **HIV** retrovirus-like particle of claim 1 and a carrier therefor.

3. The immunogenic composition of claim 2 formulated for **mucosal** or parenteral administration.

4. The immunogenic composition of claim 2 formulated for oral, anal, vaginal, or intranasal administration.

5. The immunogenic composition of claim 2 further comprising at least one other immunogenic and/or immunostimulating material.

6. The immunogenic composition of claim 5, wherein the at least one other immunostimulating material is an adjuvant.

7. The composition of claim 6, wherein the adjuvant is aluminum phosphate, aluminum hydroxide, Freund's incomplete adjuvant; or QS21.

8. A method of immunizing a host to produce a retroviral specific immune response, comprising administering to the host an immunoeffective amount of the immunogenic composition of claim 2.

L10 ANSWER 3 OF 22 USPATFULL on STN
2002:34422 Methods of inducing **mucosal** immunity.
Weiner, David B., Merion, PA, United States
Wang, Bin, Havertown, PA, United States
Ugen, Kenneth E., Philadelphia, PA, United States
The Trustees of the University of Pennsylvania, Philadelphia, PA, United States (U.S. corporation)
US 6348449 B1 20020219
APPLICATION: US 1994-357398 19941216 (8) <--
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A method of inducing a **mucosal** immune response against an antigen in an individual comprising the step of administering by topical or lavage administration to **mucosal** tissue of said individual, a composition comprising bupivacaine and a DNA molecule that comprises a nucleotide sequence that encodes said antigen, said nucleotide sequence operatively linked to regulatory sequences which control the expression of said DNA sequence, wherein: said **mucosal** tissue is selected from the group consisting of rectal, vaginal, urethral, sublingual and buccal; said DNA molecule is administered free of an infectious agent; and said DNA molecule is taken up by cells, said DNA sequence is expressed in said cells and a **mucosal** immune response is generated against said antigen.

2. The method of claim 1 wherein said DNA molecule is administered rectally.

3. The method of claim 1 wherein said DNA molecule is administered sublingually.

4. The method of claim 1 wherein said DNA molecule is administered into buccal tissue.

5. The method of claim 1 wherein said composition further comprises a DNA molecule which comprises a nucleotide sequence that encodes: a

cytokine operatively linked to regulatory sequences which control the expression of said DNA sequence; and/or a nucleotide sequence that encodes a lymphokine, said nucleotide sequence operatively linked to regulatory sequences which control the expression of said DNA sequence.

6. The method of claim 1 wherein said composition comprises a DNA molecule which comprises a nucleotide sequence that encodes a protein operatively linked to regulatory sequences which control the expression of said DNA sequence, wherein said protein is selected form the group consisting of α-interferon, gamnma-interferon, platelet derived growth factor (PDGF), GC-SF, GM-CSF, TNF, epidermal growth factor (EGF), IL-1, IL-2, IL-4, IL-6, IL-8, IL-10 and IL-12.

7. A method of inducing a **mucosal** immune response against an antigen in an individual comprising the step of administering to said individual by intravaginal topical or lavage administration, a composition comprising bupivacaine and a DNA molecule that comprises a nucleotide sequence that encodes said antigen, said nucleotide sequence operatively linked to regulatory sequences which control the expression of said DNA sequence, wherein: said DNA molecule is administered free of an infectious agent; and said DNA molecule is taken up by cells, said DNA sequence is expressed in said cells and a **mucosal** immune response is generated against said antigen.

8. The method of claim 7 wherein said composition further comprises a DNA molecule which comprises a nucleotide sequence that encodes: a cytokine operatively linked to regulatory sequences which control the expression of said DNA sequence; and/or a nucleotide sequence that encodes a lymphokine, said nucleotide sequence operatively linked to regulatory sequences which control the expression of said DNA sequence.

9. The method of claim 8 wherein said composition further comprises a DNA molecule which comprises a nucleotide sequence that encodes a protein operatively linked to regulatory sequences which control the expression of said DNA sequence, wherein said protein is selected form the group consisting of α-interferon, gamma-interferon, platelet derived growth factor (PDGF), GC-SF, GM-CSF, TNF, epidermal growth factor (EGF), IL-1, IL-2, IL-4, IL-6, IL-8, IL-10 and IL-12.

L10 ANSWER 4 OF 22 USPATFULL on STN
2001:119048 IMMUNOGENIC CONSTRUCT, PROCESS FOR ITS PREPARATION AND USE AS A VACCINE.
MANNHALTER, JOSEF W., VIENNA, Euratom
LEIBL, HEINZ, VIENNA, Euratom
EIBL, MARTHA, VIENNA, Euratom
US 2001009669 A1 20010726
APPLICATION: US 1997-973397 A1 19971212 (8) <--
WO 1996-EP2098 19960515 None PCT 102(e) date <--
PRIORITY: DE 1995-19521705 19950614
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. Immunogenic construct comprising as components: (i) an inactive flavivirus or a derivative thereof, and (ii) at least one immunogenic component which is bound to the flavivirus and/or the derivative thereof.

2. Construct according to claim 1, characterized in that it is an inactivated flavivirus.

3. Construct according to claim 2, characterized in that the flavivirus is chemically or physically inactivated.

4. Construct according to one or more of the above claims, characterized in that the flavivirus is an attenuated flavivirus and/or a derivative of an attenuated flavivirus.

5. Construct according to one or more of the above claims, characterized in that the flavivirus is a TBE virus, preferably FSME virus of the western subtype, and/or a derivative of a TBE virus.

6. Construct according to claims 1 to 5, characterized in that the immunogenic component is a protein, a polypeptide, a polysaccharide or a nucleic acid and/or a combination of two or more of the above named components or an inactive microorganism.

7. Construct according to claim 6, characterized in that the protein, the polypeptide, the polysaccharide or the nucleic acid is derived from

a virus, bacterium, a fungus or a parasite.

8. Construct according to claim 6 or 7, characterized in that the immunogenic component is derived from a virus selected from the group **HIV**, hepatitis, influenza or herpes.

9. Construct according to claim 6 or 7, characterized in that the immunogenic component is derived from a bacterium selected from the group Bordetella, Haemophilus, Borrelia, Pseudomonas, Corynebacteria, Mycobacteria, Streptococci, Salmonella, Pneumococci, Staphylococci, Clostridia or Helicobacter.

10. Construct according to one or more of the above claims, characterized in that the components are bound to each other via a covalent bond.

11. Construct according to claim 10, characterized in that the construct is adsorbed to a carrier.

12. Construct according to claims 1 to 9, characterized in that the components are bound by adsorption and are preferably adsorbed to a carrier.

13. Method for the production of an immunogenic construct according to claims 1 to 11, characterized by the following steps: (i) treating the inactive flavivirus or a derivative thereof and/or the immunogenic component with an activator suitable for covalent bonding, (ii) optionally separating excess activator, (iii) incubating the treated inactivated flavivirus and/or a derivative thereof and/or the treated immunogenic component, optionally with a non-treated flavivirus and/or derivative thereof, or a non-treated immunogenic component, under conditions which permit the formation of a covalent bond, and (iv) purifying the construct.

14. Method according to claim 13, characterized in that the activator for the covalent bonding is a homo- or hetero-bifunctional cross-linker.

15. Method according to claim 13 or 14, characterized in that the activator for the covalent bonding is separated by means of dialysis, centrifugation, filtration, precipitation or with the aid of a chromatographic method.

16. Method according to claim 13, characterized in that the purification of the construct is conducted by means of centrifugation, filtration, precipitation, dialysis or with the aid of a chromatographic method.

17. Method for the production of a construct according to the claims 1 to 9 and 12, characterized in that it comprises the following steps: (i) incubating the inactivated flavivirus or a derivative thereof and an immunogenic component together with an adsorbing carrier material under conditions which permit the adsorption of the components to the carrier material, and (ii) separating the construct from the non-adsorbed components.

18. Method according to claim 17, characterized in that the carrier material is a metal, a poorly soluble or colloidal metal compound or a polymer compound or consists of lipid vesicles.

19. Method according to claim 17 or 18, characterized in that the construct is separated by means of centrifugation, filtration or with the aid of a chromatographic method and optionally further purified.

20. Immunogenic construct comprising as components: (i) a nucleic acid sequence for an inactivated flavivirus or a derivative thereof with adjuvant function in connection with (ii) a nucleic acid for an immunogenic component, and (iii) regulation sequences which ensure the expression of the nucleic acids sequences in a host.

21. Immunogenic construct, characterized in that it is present as a viral or bacterial expression vector, as a recombinant phage or as naked DNA and/or RNA.

22. Immunogenic construct according to claim 21, characterized in that it is present as an expression vector in vaccinia virus.

23. Vaccine, characterized by an immunogenic construct according to claims 1 to 12 and 20 to 22, together with a suitable excipient.

24. Vaccine according to claim 23, wherein an immune response against

flavivirus or a derivative thereof is induced and the immune response against the immunogenic component is simultaneously enhanced.

25. Polyvalent vaccine, characterized in that it comprises constructs according to the claims 1 to 12 and 20 to 22 with different immunogenic components.

26. Pharmaceutical preparation, characterized in that it comprises constructs according to the claims 1 to 12 and 20 to 22 together with a suitable diluent.

27. Specific immunoglobulin preparation obtainable by immunizing a mammal with a construct according to the claims 1 to 12 and 20 to 22 and subsequently isolating the immunoglobulins from blood, serum, plasma, plasma fractions or **mucosal** secretions.

28. Immunoglobulin preparation according to claim 27, characterized in that the preparation essentially comprises IgG or **IgA**.

29. Immunoglobulin preparation according to claim 27 or 28, characterized in that this is subjected to a method for inactivating viruses which may be present.

30. Kit for the production of a construct according to claim 1 to 12 comprising: (i) the inactivated flavivirus or a derivative thereof, (ii) the immunogenic component as well as (iii) an activator suitable for the covalent bonding or an adsorbing carrier material.

31. Kit for the production of a construct according to claim 1 to 12 comprising: (i) the immunogenic component, and (ii) the inactive flavivirus and/or a derivative thereof suitable for binding to (i).

32. Reagent for the production of a construct according to claim 1 to 12, containing the inactive flavivirus and/or a derivative thereof suitable for binding to an immunogenic component.

33. Reagent according to claim 32, characterized in that it is present in solution, as a suspension or as a lyophilizate.

34. Use of an inactivated flavivirus or derivative thereof for the production of an adjuvant or carrier.

L10 ANSWER 5 OF 22 USPATFULL on STN
2000:97977 **Mucosal** administration of substances to mammals.
Betbeder, Didier, Aucamville, France
Etienne, Alain, Toulouse, France
de Miguel, Ignacio, Toulouse, France
Kravtzoff, Roger, Fourquevaux, France
Major, Michel, Toulouse, France
Biovector Therapeutics, S.A., Labege Cedex, France (non-U.S. corporation)
US 6096291 20000801
APPLICATION: US 1996-774920 19961227 (8) <--
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A method for the **mucosal** administration of a vaccine against a pathogen to a mammal, the method comprising contacting a **mucosal** surface of the mammal with an antigen in combination with a Biovector core, wherein the Biovector core comprises a natural polymer, or a derivative or a hydrolysate of a natural polymer, or a mixture thereof, and wherein the core is uncoated, or is partially or completely coated with no more than one layer, the layer comprising a lipid compound covalently bonded to the core, or an amphiphilic compound.

2. The method of claim 1, wherein the natural polymer is selected from the group consisting of a cross-linked polysaccharide, a cross-linked oligosaccharide, a derivative or hydrolysate of a cross-linked polysaccharidec or a cross-linked oligosaccharide, and a mixture thereof.

3. The method of claim 2, wherein the cross-linked polysaccharide and cross-linked oligosaccharide are selected from the group consisting of starch, dextran, dextrin, and maltodextrin.

4. The method of claim 2, wherein 0 to 2 milliequivalents of ionic charge per gram is grafted to the cross-linked polysaccharide or cross-linked oligosaccharide.

5. The method of claim 4, wherein the ionic charge is a positive charge.

6. The method of claim 5, wherein the positive charge is due to the presence of a cationic or basic group selected from the group consisting of a quaternary ammonium group, a primary amine, a secondary amine, and a tertiary amine.

7. The method of claim 5, wherein the positive charge is due to the presence of a quaternary ammonium group.

8. The method of claim 5, wherein the positive charge is due to the presence of a ligand selected from the group consisting of choline, 2-hydroxypropyltrimethylammonium, 2-dimethylaminoethanol, 2-diethylarninoethanol, 2-dimethylaminoethylamine, and 2-diethylaminoethylamine and an amino acid.

9. The method of claim 4, wherein the ionic charge is a negative charge.

10. The method of claim 9, wherein the negative charge is due to the presence of a an anionic or acidic group selected from phosphate, a sulfate, and carboxylate.

11. The method of claim 9, wherein the negative charge is due to the presence of a phosphate group.

12. The method of claim 2, wherein the cross-linked polysaccharide or cross-linked oligosaccharide is coated partially or completely with a layer of an amphiphilic compound.

13. The method of claim 12 wherein the amphiphilic compound is a phospholipid or a ceramide.

14. The method of claim 13 wherein the phospholipid is selectcd from the group consisting of phosphatidyl choline, phosphatidyl hydroxycholine, phosphatidyl ethanolamine, phosphatidyl serine, and phosphatidyl glycerol.

15. The method of claim 1, wherein the diameter of the Biovector is 20-200 nm.

16. The method of claim 1, wherein the diameter of the Biovector is 20-100 nm.

17. The method of claim 1, wherein the cross-linked polysaccharide or cross-linked oligosaccharide binds non-specifically to the **mucosal** surface.

18. The method of claim 1 wherein the Biovector is dispersed.

19. The method of claim 1, wherein the Biovector is dried.

20. The method of claim 19, wherein the dried Biovector is resuspended.

21. The method of claim 1, wherein the pathogen is selected from the group consisting of a virus, a bacterium, a yeast, and a fungus.

22. The method of claim 21, wherein the virus is selected from the group consisting of an influenza virus, a cytomegalovirus, **HIV**, a papilloma virus, a respiratory syncytial virus, a poliomyelitis virus, a pox virus, a measles virus, an arbor virus, a Coxsackie virus, a herpes virus, a hantavirus, a hepatitis virus, a lyme disease virus, a mumps virus, and a rotavirus.

23. The method of claim 22, wherein the virus is an influenza virus.

24. The method of claim 22, wherein the virus is **HIV**.

25. The method of claim 21, wherein the bacterium is selected from the group consisting of a member of the genus Neisseria, Aerobacter, Pseudomonas, Porphyromonas, Salmonella, Escherichia, Pasteurella, Shigella, Bacillus, Helibacter, Corynebacterium, Clostridium, Mycobacterium, Yersinia, Staphylococcus; Bordetelia, Brucelia, Vibrio, and Streptococcus.

26. The method of claim 21, wherein the pathogen is a member of a genus selected from the group consisting of Plasmodium, Schisostoma, and Candida.

27. The method of claim 1, wherein the antigen is a biological molecule.

28. The method of claim 27, wherein the biological molecule is selected from the group consisting of an amino acid, an oligopeptide, a peptide, a protein, a glycoprotein, and a lipoprotein.

29. The method of claim 1, wherein more than one antigen is administered in combination with the Biovector.

30. The method of claim 2, wherein the antigen is located in the inner core of the cross-linked polysaccharide or cross-linked oligosaccharide.

31. The method of claim 2, wherein the antigen is located at the outer surface of the cross-linked polysaccharide or cross-linked oligosaccharide.

32. The method of claim 12, wherein the antigen is located in the inner core of the amphiphilic compound layer.

33. The method of claim 12, wherein the antigen is located at the outer surface of the layer.

34. The method of claim 1, wherein the antigen is added to the Biovector prior to administration to the mammal.

35. The method of claim 1, wherein the antigen and the Biovector are mixed together at the time of administration to the mammal.

36. The method of claim 1, wherein the **mucosal** surface is selected from the group consisting of a nasal, buccal, oral, vaginal, ocular, auditory, pulmonary tract, urethral, digestive tract, and rectal surface.

37. The method of claim 36, wherein the **mucosal** surface is selected from the group consisting of a nasal, vaginal, and ocular surface.

L10 ANSWER 6 OF 22 USPATFULL on STN
2000:80416 **Human immunodeficiency virus** type 1 nucleic acids devoid of long terminal repeats capable of encoding for non-infectious, immunogenic, retrovirus-like particles.
Rovinski, Benjamin, Thornhill, Canada
Cao, Shi-Xian, Etobicoke, Canada
Yao, Fei-Long, North York, Canada
Persson, Roy, North York, Canada
Klein, Michel H., Willowdale, Canada
Connaught Laboratories Limited, Toronto, Canada (non-U.S. corporation)
US 6080408 20000627
APPLICATION: US 1995-482810 19950607 (8) <--
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed:
1. A nucleic acid molecule, comprising: a modified **human immunodeficiency virus** (**HIV**) genome, deficient in long terminal repeats (LTRs), containing the gag, pol and env genes in their natural genomic arrangement and means for expression operatively connected to said modified **HIV** genome for production of gene products in cells to produce non-infectious, immunogenic, non-replicating **HIV** retrovirus-like particles comprising, in an assembly, the gag, pot and env gene products, wherein: (1) at least one codon in the gag gene has been mutated to effect modification to the gag gene product in the first Cys-His box only of the gag gene product by replacing at least one amino acid residue in the first Cys-His box contributing to gag-dependent genomic viral RNA packaging into said **HIV** retrovirus-like particles to effect reduction of gag-dependent genomic viral RNA packaging into the particles while retaining the immunogenicity of the **HIV** retrovirus-like particles; (2) codons in the pol gene encoding a portion of the pol gene product contributing to reverse transcriptase activity have been deleted to substantially eliminate reverse transcriptase activity of the pol gene product in the **HIV** retrovirus-like particles; (3) codons in the pol gene encoding a portion of the pol gene product contributing to integrase activity have been deleted to substantially eliminate integrase activity of the pol gene product in the **HIV** retrovirus-like particles; and (4) codons in the pol gene encoding a portion of the pol gene product contributing to RNase H activity have been deleted to substantially eliminate RNase H activity of the pol gene product in the **HIV** retrovirus-like particles.

2. The nucleic acid molecule of claim 1 wherein said nucleic acid molecule comprises a SacI (678) to XhoI (8944) **HIV-1**$_{LAI}$

restriction fragment.

3. The nucleic acid molecule of claim 1, wherein said molecule is deficient in the primer binding site (PBS) and/or an RNA packaging signal.

4. The nucleic acid molecule of claim 1, wherein the reduction of gag-dependent RNA packaging is effected by mutagenesis of a region thereof encoding at least one amino acid contained within a region of the gag gene product corresponding to Cys^{392} to Cys^{395} of the **HIV**-1 LAI isolate, or a corresponding region of other **HIV**-1 isolates.

5. The nucleic acid molecule of claim 4, wherein a codon encoding Cys^{392} and/or Cys^{395} is replaced by a codon encoding serine.

6. The nucleic acid molecule of claim 5, wherein codons encoding both Cys^{392} and Cys^{395} are replaced by codons encoding serine.

7. The nucleic acid molecule of claim 1, wherein the **HIV** retrovirus is selected from the group consisting of **HIV**-1 and **HIV**-2.

8. The nucleic acid molecule of claim 1, wherein the env gene is an LAI env gene, an MN env gene or an env gene from a primary **HIV**-1 isolate.

9. An immunogenic composition capable of eliciting a retroviral specific immune response, comprising the nucleic acid molecule of claim 1 and a carrier therefor.

10. The immunogenic composition of claim 9 formulated for **mucosal** or parenteral administration.

11. The immunogenic composition of claim 9 formulated for oral, anal, vaginal, or intranasal administration.

12. The immunogenic composition of claim 9 further comprising at least one other immunogenic and/or immunostimulating material.

13. The immunogenic composition of claim 9, further comprising an adjuvant.

14. The composition of claim 13, wherein the adjuvant is aluminum phosphate, aluminum hydroxide, Freund's incomplete adjuvant, or QS21.

15. A method of immunizing a host to produce a retroviral specific immune response, comprising administering to the host an immunoeffective amount of the immunogenic composition of claim 9.

16. The nucleic acid molecule of claim 1, wherein the at least a part of the pol gene encoding reverse transcriptase is contained between nucleotides 2586 and 4265 of the pol gene of **HIV**-1 isolate LAI or the corresponding region of other **HIV** pol genes.

17. The nucleic acid molecule of claim 1, wherein the at least a part of the pol gene encoding integrase is contained between nucleotides 4266 and 5129 of the pol gene of **HIV**-1 isolate LAI or the corresponding region of other **HIV** pol genes.

18. The nucleic acid molecule of claim 1, wherein said modified retroviral genome includes a heterologous nucleic acid insert encoding at least one non-retroviral, non-mammalian antigenic marker, wherein said marker, when presented in the context of said **HIV** retrovirus-like particle, is capable of generating an immune response specific to said antigenic marker when the particle is administered to a host.

19. The nucleic acid molecule of claim 18, wherein the heterologous nucleic acid insert is inserted into the gag gene at the PstI site at nucleotide 1415 of the gag gene of **HIV**-1 LAI isolate or the corresponding location of other **HIV** gag genes.

20. The nucleic acid molecule of claim 19 wherein the heterologous nucleic acid insert comprises from 1 to 4 copies of a DNA sequence selected from the group consisting of: (a) 5' GCATTCGACACTAGAAATAGAATAATAGAAGTTGAAAAT 3' (SEQ ID NO:5); and (b) 3' CGTAAGCTGTGATCTTTATCTTATTATCTTCAACTTTTA 5' (SEQ ID NO: 6).

21. The nucleic acid molecule of claim 1 wherein said env gene has been modified to provide a modified env gene product in the **HIV** retrovirus-like particles in which endogenous anchoring function of env has been replaced by a non-retroviral antigenic anchor marker sequence

operatively connected to the env gene product to anchor said env gene product to the **HIV** retrovirus-like particle, and wherein said marker, when presented in the context of the retrovirus-like product, is capable of generating an immune response specific to said antigenic marker when the particle is administered to a host.

22. The nucleic acid molecule of claim 21 wherein the antigenic anchor sequence comprises a DNA sequence selected from the group consisting of: (a) 5' TGGATCCTGTGGATTCCTTTGCCATATCATGCTTTTTGCTTTG TGTTGTTTTGCTGGGGTTCATCATGTGG 3' (SEQ ID NO: 7); and (b) 3' ACCTAGGACACCTAAAGGAAACGGTATAGTACGAAAAACGAAA CACAACAAAACGACCCCAAGTAGTACACC 5' (SEQ ID NO: 8).

23. The nucleic acid molecule of claim 21 wherein the antigenic anchor sequence includes a DNA sequence selected from the group consisting of: (a) 5' TCAACAGTGGCAAGTTCCCTAGCACTGGCAATCAT GATAGCTGTGCTATCTTTTTGGATGTGTT CCAATGGGTCATTGCAG 3' (SEQ ID NO: 9); and (b) 3' AGTTGTCACCGTTCAAGGGATCGTGACCGTTAGTACTATCGA CCAGATAGAAAAACCTACACAAGGTTACC CAGTAACGTC 5' (SEQ ID NO: 10).

24. The nucleic acid molecule of claim 21 wherein the antigenic anchor sequence includes a DNA sequence selected from the group consisting of: (a) 5' TGGATCCTGTGGATTTCCTTTGCCATATCATGCTTTTTGC TTTGTGTTGTTTGCTGGGGTTCATCATGTGGGCCTGCCAAAAAGGCA ACGGTGCAACATTTGCATTTGATAGTAAAGAAGAGTGGTGCAGAGA GAAAAAAGAGCAGTGGGAA 3' (SEQ ID NO. 11); and (b) 3' ACCTAGGACACCTAAAGGAAACGGTATAGTACGAAAAACG AAACACAACAAACGACCCCAAGTAGTACACCCGGACGGTTTTTCCG TTGAATCCACGTTGTAAACGTAAACTATCATTTCTTCTCACCACGTCT CTCTTTTTTCTCGTCACCCTT 5' (SEQ ID NO:12).

L10 ANSWER 7 OF 22 USPATFULL on STN
1999:145984 Oral or intranasal vaccines using hydrophobic complexes having proteosomes and lipopolysaccharides.
Lowell, George H., 6303 Western Run Dr., Baltimore, MD, United States 21215
US 5985284 19991116
APPLICATION: US 1996-677302 19960709 (8) <--
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. An immunogenic hydrophobic complex consisting essentially of proteosomes and at least one non-detoxified antigenic lipopolysaccharide.

2. The immunogenic hydrophobic complex of claim 1 wherein the lipopolysaccharide is isolated from Shigella.

3. The immunogenic hydrophobic complex of claim 2 wherein the Shigella is selected from the group consisting of S. flexneri 2a and Shigella sonnei or mixtures thereof.

4. The immunogenic hydrophobic complex of claim 1 wherein the proteosomes are derived from N. meningiditis.

5. The immunogenic hydrophobic complex of claim 1 wherein the proteosomes are derived from N. gonorrhea.

6. A vaccine comprising the immunogenic hydrophobic complex according to any one of claims 1, 2, 3, 4 and 5 and a carrier.

7. A method for providing enhanced immunogenicity comprising administering the vaccine of claim 6 to a subject parenterally, orally, intranasally or topically.

8. A method of achieving immunity by administering the vaccine of claim 6 to a subject parenterally, orally, intranasally or topically to impart immunity.

9. A method of achieving immunity according to claim 8 wherein the immunity is to gram negative bacterial infection.

10. A method of achieving immunity according to claim 9 wherein the immunity is to neisserial infection.

11. A method of achieving immunity according to claim 10 wherein the immunity is to gonococcal infection.

12. A method of achieving immunity according to claim 10 wherein the

immunity is to meningococcal infection.

13. A method of achieving immunity according to claim 8 wherein the immunity is to shigellosis.

14. A method of achieving immunity according to claim 13 wherein the shigellosis immunity is to Shigella flexneri 2a.

15. A method of achieving immunity according to claim 13 wherein the shigellosis immunity is to Shigella sonnei.

16. A method of achieving immunity according to claim 8 by administering the vaccine to **mucosal** surfaces selected from the group of respiratory, gastrointestinal, vaginal, nasal, rectal and oral mucosa.

L10 ANSWER 8 OF 22 USPATFULL on STN
1999:113630 Non-infectious, replication-defective, self-assembling **HIV**-1 viral particles containing antigenic markers in the gag coding region.
Rovinski, Benjamin, Thornhill, Canada
Cao, Shi-Xian, Etobicoke, Canada
Yao, Fei-Long, North York, Canada
Persson, Roy, North York, Canada
Klein, Michel H., Willowdale, Canada
Connaught Laboratories Limited, North York, Canada (non-U.S. corporation)
US 5955342 19990921
APPLICATION: US 1994-290105 19940815 (8) <--
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A non-infectious, non-replicating **HIV** retrovirus-like particle containing a heterologous antigenic marker, comprising an assembly of: (a) an env gene product; (b) a pol gene product; (c) a gag gene product; and, (d) at least one non-retroviral, non-mammalian heterologous antigenic marker, wherein said marker, when presented in the context of the retrovirus-like particle, is capable of generating an immune response to said antigenic marker when the particle is administered to a host, said particle being encoded by a modified **HIV** retroviral genome deficient in long terminal repeats (LTRs) and containing gag, pol, and env in their natural genomic arrangement and a heterologous nucleic acid insert encoding said at least one antigenic marker.

2. The retrovirus-like particle of claim 1, wherein said at least one antigenic marker has between 5 and 100 amino acid residues.

3. The retrovirus-like particle of claim 2, wherein said at least one antigenic marker has 10 to 75 amino acid residues.

4. The retrovirus-like particle of claim 2 or 3, wherein the at least one antigenic marker comprises at least one antigenic epitope from tobacco mosaic virus coat protein.

5. The retrovirus-like particle of claim 4, wherein the at least one antigenic epitope includes an amino acid sequence AFDTRNRIIEVEN (SEQ ID No: 1) or a portion, variation or mutant thereof capable of eliciting antibodies that recognize the sequence AFDTRNRIIEVEN (SEQ ID No: 1).

6. The retrovirus-like particle of claim 2, wherein the at least one antigenic marker is contained within the gag gene product to form a hybrid gag gene product having the particle-forming characteristics of an unmodified gag gene product.

7. The retrovirus-like particle of claim 6, wherein said at least one antigenic marker is inserted into the gag gene product at an antigenically-active insertion site.

8. The retrovirus-like particle of claim 7, wherein said insertion site is located between amino acid residues 210 and 211 of the gag gene product of the **HIV**-1 LAI isolate or the corresponding location of other **HIV** gag gene products.

9. The retrovirus-like particle of claim 8, wherein said at least one antigenic marker comprises from 1 to 4 tandem copies of the amino acid sequence AFDTRNRIIEVEN (SEQ ID No: 1) or a portion, variation or mutant thereof capable of eliciting antibodies that recognize the sequence AFDTRNRIIEVEN (SEQ ID No: 1).

10. The retrovirus-like particle of claim 1, wherein the human retrovirus is selected from the group consisting of **HIV**-1 and **HIV**-2.

11. The retrovirus-like particle of claim 10, wherein the human retrovirus is **HIV**-1 and the env gene product is an LAI env gene product, an MN env gene product or an env gene product from a primary **HIV**-1 isolate.

12. An immunogenic composition capable of eliciting a retroviral specific immune response and a specific immune response against a non-retroviral marker, comprising the retrovirus-like particle of claim 1 and a carrier therefor.

13. The immunogenic composition of claim 12 formulated for **mucosal** or parenteral administration.

14. The immunogenic composition of claim 12 formulated for oral, anal, vaginal, or intranasal administration.

15. The immunogenic composition of claim 13 further comprising at least one other immunogenic or immunostimulating material.

16. The composition of claim 15, wherein the at least one other immunostimulating material is an adjuvant.

17. The composition of claim 16, wherein the adjuvant is selected from the group consisting of aluminum phosphate, aluminum hydroxide, Freund's incomplete adjuvant, and QS21.

18. A method of immunizing a host to produce a retroviral specific immune response and a specific immune response against the antigenic marker, comprising administering to the host an immunoeffective amount of the immunogenic composition of claim 12.

19. A non-infectious, non-replicating **HIV**-1 retrovirus-like particle containing a heterologous antigenic marker, comprising an assembly of: (a) an env gene product; (b) a pol gene product; (c) a gag gene product; and, (d) a non-retroviral, non-mammalian heterologous antigenic marker comprising from one to four tandemly linked copies of the amino acid sequence AFDTRNRIIEVEN (SEQ ID NO: 1) inserted into the gag gene product between amino acids 210 and 211 of the **HIV**-1 LAI isolate, wherein said marker, when presented in the context of the retrovirus-like particle, is capable of generating an immune response to said antigenic marker when the particle is administered to a host, said particle being encoded by a modified **HIV** retroviral genome deficient in long terminal repeats (LTRs) and containing gag, pol, and env in their natural genomic arrangement and a heterologous nucleic acid insert encoding said antigenic marker.

L10 ANSWER 9 OF 22 USPATFULL on STN
1999:109976 Tandem synthetic **HIV**-1 peptides.
Sia, Charles D. Y., Thornhill, Canada
Chong, Pele, Richmond Hill, Canada
Klein, Michel H., Willowdale, Canada
Connaught Laboratories Limited, North York, Canada (non-U.S. corporation)
US 5951986 19990914
APPLICATION: US 1995-467881 19950606 (8) <--
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. An immunogenic composition, comprising at least one synthetic peptide which is selected from the group consisting of: (i) a synthetic peptide, which consists of at least one amino acid sequence which contains a T-cell epitope of the gag protein of a **human immunodeficiency virus** (**HIV**) isolate and is selected from the group consisting of P24N, P24L, P24M and P24H and having the respective amino acid sequences QMREPRGSDIAGTTSTL (SEQ ID NO: 70), EEMMTACQGVGGPGHK (SEQ ID NO: 73), GHKARVLAEAMSQVT (SEQ ID NO: 76) and PIVQNIQGQMVHQAI(SEQ ID NO: 79) linked at the C-terminal end thereof, to at least one amino acid sequence which is a B-cell epitope of the V3 loop of the envelope protein of an **HIV** isolate, (ii) a synthetic peptide, which consists of at least one amino acid sequence which contains a T-cell epitope of the gag protein of a **human immunodeficiency virus** (**HIV**) isolate linked at the C-terminal end thereof to at least one amino acid sequence which contains a B-cell epitope and consisting of a hybrid V3 loop sequence from at least two different **HIV**-1 isolates; (iii) a synthetic peptide, which consists of at least one amino acid sequence which contains a T-cell epitope of the gag protein of a **human immunodeficiency virus** (**HIV**) isolate linked at the C-terminal end thereof to at least one amino acid sequence which contains a B-cell

epitope comprising a consensus sequence of the V3 loop of at least two **HIV**-1 primary isolates; (iv) a synthetic peptide, which consists of at least one amino acid sequence which contains a T-cell epitope of the gag protein of a **human immunodeficiency virus** (**HIV**) isolate linked at the C-terminal end thereof to at least two amino acid sequences which contain a B-cell epitope, said B-cell epitope containing amino acid sequences each consisting of a V3 loop sequence from a different **HIV**-1 isolate or **HIV**-isolate consensus sequences; (v) a synthetic peptide, which consists of at least one amino acid sequence which contains a T-cell epitope of the gag protein of a **human immunodeficiency virus** (**HIV**) isolate linked at the C-terminal end thereof to at least one amino acid sequence which contain a B-cell epitope of the **gp41** protein of an **HIV** isolate and containing the amino acid sequence X_1 LKDWX_2 wherein X_1 is E, A, G or Q and X_2 is A or T or an amino acid sequence capable of eliciting an **HIV**-specific antiserum and recognizing the amino acid sequence X_1 LKDWX_2, and (vi) a synthetic peptide, having a plurality of individual synthetic peptides linked at the C-terminus of each said individual linear synthetic peptide to form a multimeric molecule, each said individual synthetic peptide having an amino acid sequence which contains a T-cell epitope of a gag or envelope protein of a **human immunodeficiency virus** (**HIV**) isolate linked to an amino acid sequence which contains a B-cell epitope of a gag or envelope protein of an **HIV** isolate, and a pharmaceutically-acceptable carrier therefor.

2. The immunogenic composition of claim 1 comprising a plurality of said synthetic peptides selected to provide an immune response to a plurality of immunologically-distinct **HIV**-1 isolates.

3. The immunogenic composition of claim 2 wherein said plurality of said synthetic peptides are further selected to provide said immune response in a plurality of hosts differentially responsive to T-cell epitopes.

4. The immunogenic composition of claim 3 wherein said plurality of synthetic peptides comprises: GPKEPFRDYVDRFYKNKRKRIHIGPGRAFYTTKN (CTLB-36) (SEQ ID NO: 3); KQIINMWQEVEKAMYANKRKRIHIGPGRAFTTTKN (CTLB-91) (SEQ ID NO: 23); GPKEPFRDYVDRFYKNTRKSIHIGPGRAFYATGEIIG (BX08) (SEQ ID NO: 43).

5. The immunogenic composition of claim 4 wherein said plurality of synthetic peptides further comprises: GPKEPFRDYVDRFYKPGELDKWASGPGKQIINMW QEVEKAMYA (MPK-2) (SEQ ID NO: 95).

6. The immunogenic composition of claim 1 formulated for **mucosal** or parenteral administration.

7. The immunogenic composition of claim 6 further comprising at least one other immunogenic or immunostimulating material.

8. The composition of claim 7 wherein the at least one other material is an adjuvant.

9. The composition of claim 8, wherein the adjuvant is aluminum phosphate or aluminum hydroxide.

L10 ANSWER 10 OF 22 USPATFULL on STN
1999:40590 Nucleic acid molecules encoding non-infectious, non-replicating, **HIV** retrovirus-like particles containing heterologous antigenic anchor sequences.
Rovinski, Benjamin, Thornhill, Canada
Cao, Shi-Xian, Etobicoke, Canada
Yao, Fei-Long, North York, Canada
Persson, Roy, North York, Canada
Klein, Michel H., Willowdale, Canada
Connaught Laboratories Limited, Toronto, Canada (non-U.S. corporation)
US 5889176 19990330
APPLICATION: US 1996-761209 19961206 (8) <--
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A nucleic acid molecule encoding a non-infectious, non-replicating, **human immunodeficiency virus** (**HIV**) retrovirus-like particle containing a heterologous antigenic anchor sequence, comprising an assembly of: (a) a gag gene product; (b) a pol gene product; and (c) a modified env gene product comprising a non-retroviral, heterologous, antigenic, anchor sequence, wherein said anchor sequence replaces the endogenous anchoring functions of the env gene product; wherein said particle is encoded by a modified **HIV** genome deficient in long

terminal repeats (LTRs), containing the gag, pol, and env genes in their natural genomic arrangement, and a heterologous nucleic acid insert encoding said heterologous antigenic anchor sequence, wherein said sequence, when presented in the context of the retrovirus-like particle, is capable of generating an immune response specific to said antigenic anchor sequence when the particle is administered to a host.

2. The nucleic acid molecule of claim 1, wherein the nucleic acid insert encoding the anchor sequence contains between 15 and 300 nucleotides.

3. The nucleic acid molecule of claim 2, wherein the nucleic acid insert encoding the anchor sequence contains between 15 and 225 nucleotides.

4. The nucleic acid molecule of claim 1, wherein the heterologous nucleic acid insert encodes at least a portion of a transmembrane component of a membrane-spanning protein.

5. The nucleic acid molecule of claim 4, wherein the heterologous nucleic acid insert encodes a membrane-spanning glycoprotein.

6. The nucleic acid molecule of claim 5, wherein the heterologous nucleic acid insert encodes an influenza virus glycoprotein.

7. The nucleic acid molecule of claim 6, wherein the heterologous nucleic acid insert encodes a human influenza virus glycoprotein.

8. The nucleic acid molecule of claim 6, wherein the heterologous nucleic acid insert encodes an amino acid sequence having SEQ ID NO.: 2, or a portion, variant, or mutant thereof, capable of eliciting antibodies specific to said amino acid sequence.

9. The nucleic acid molecule of claim 1, wherein the heterologous nucleic acid insert comprises a nucleic acid sequence selected from the group consisting of SEQ ID NO.: 7 and SEQ ID NO.: 8.

10. The nucleic acid molecule of claim 6, wherein the heterologous nucleic acid insert encodes an avian influenza virus glycoprotein.

11. The nucleic acid molecule of claim 10, wherein the heterologous nucleic acid insert encodes an amino acid sequence having SEQ ID NO.: 2, or a portion, variant, or mutant thereof, capable of eliciting antibodies specific to said amino acid sequence.

12. The nucleic acid molecule of claim 10, wherein the heterologous nucleic acid insert comprises a nucleic acid sequence selected from the group consisting of SEQ ID NO.: 9 and SEQ ID NO.: 10.

13. The nucleic acid molecule of claim 10, wherein the heterologous nucleic acid insert encodes an amino acid sequence having SEQ ID NO.: 4, or a portion, variant, or mutant thereof, capable of eliciting antibodies specific to said amino acid sequence.

14. The nucleic acid molecule of claim 1, wherein the heterologous nucleic acid insert comprises a nucleic acid sequence selected from the group consisting of SEQ ID NO.: 11 and SEQ ID NO.: 12.

15. The nucleic acid molecule of claim 1, wherein said heterologous nucleic acid insert is inserted into the env gene adjacent to, and upstream of, nucleotides encoding functional cleavage sites of the env gene product.

16. The nucleic acid molecule of claim 15, wherein said heterologous nucleic acid insert is inserted between nucleotides 7777 and 7778 of the **HIV-1**$_{LAI}$ env gene product, or the corresponding location in other **HIV** env gene products.

17. The nucleic acid molecule of claim 1, wherein said modified **HIV** genome is deficient in the primer binding site.

18. An immunogenic composition comprising the nucleic acid molecule of claim 1, and a carrier therefor, wherein said composition is capable of eliciting a retroviral-specific immune response and an anchor sequence-specific immune response.

19. The immunogenic composition of claim 18 formulated for **mucosal** or parenteral administration.

20. The immunogenic composition of claim 18 formulated for oral, anal, vaginal, or intranasal administration.

21. The immunogenic composition of claim 19 further comprising at least one other immunogenic or immunostimulating material.

22. The composition of claim 21, wherein the at least one other immunostimulating material is an adjuvant.

23. The composition of claim 22, wherein the adjuvant is selected from the group consisting of aluminum phosphate, aluminum hydroxide, Freund's incomplete adjuvant, and QS21.

24. A method of immunizing a host to produce a retroviral-specific immune response and an anchor sequence-specific immune response, comprising administering to the host the immunogenic composition of claim 18.

25. A nucleic acid molecule encoding a non-infectious, non-replicating, **human immunodeficiency virus** (**HIV**) retrovirus-like particle containing a heterologous antigenic anchor sequence, comprising an assembly of: (a) a gag gene product; (b) a pol gene product; and (c) a modified env gene product comprising a non-retroviral, heterologous, antigenic, anchor sequence, wherein said anchor sequence replaces the endogenous anchoring functions of the env gene product; wherein said particle is encoded by a modified **HIV** genome deficient in long terminal repeats (LTRs), containing the gag, pol, and env genes in their natural genomic arrangement, and a heterologous nucleic acid insert encoding said heterologous antigenic anchor sequence, wherein said heterologous nucleic acid insert is selected from the group consisting of SEQ ID NO.: 7, SEQ ID NO.: 8, SEQ ID NO.: 9, SEQ ID NO.: 10, SEQ ID NO.: 11, and SEQ ID NO.: 12, and wherein said heterologous nucleic acid insert is inserted between nucleotides 7777 and 7778 of the **HIV**-1_{LAI} env gene product, wherein said sequence, when presented in the context of the retrovirus-like particle, is capable of generating an immune response specific to said antigenic anchor sequence when the particle is administered to a host.

26. An expression vector comprising the nucleic acid molecule of claim 1.

27. The expression vector as claimed in claim 26 which is pMTHIVHA2-701.

28. The expression vector as claimed in claim 26 which is pMTHIVmHA2.

29. The expression vector as claimed in claim 26 which is pMTHIVMNmHA2-5.

L10 ANSWER 11 OF 22 USPATFULL on STN
1999:30609 Genetically engineered **human immunodeficiency virus**-like particles with modified chimeric envelope glycoproteins containing influenza virus transmembrane spanning domains.
Rovinski, Benjamin, Thornhill, Canada
Cao, Shi-Xian, Etobicoke, Canada
Yao, Fei-Long, North York, Canada
Persson, Roy, North York, Canada
Klein, Michel H., Willowdale, Canada
Connaught Laboratories Limited, North York, Canada (non-U.S. corporation)
US 5879925 19990309
APPLICATION: US 1996-761828 19961206 (8) <--
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A non-infectious, non-replicating, **HIV** retrovirus-like particle containing a heterologous antigenic anchor sequence, comprising an assembly of: (a) a gag gene product; (b) a pol gene product; and (c) a modified env gene product comprising a non-retroviral, heterologous, antigenic, anchor sequence, wherein said anchor sequence replaces the endogenous anchoring functions of the env gene product; wherein said particle is encoded by a modified **HIV** genome deficient in long terminal repeats (LTRs), containing the gag, pol, and env genes in their natural genomic arrangement, and a heterologous nucleic acid insert encoding said heterologous antigenic anchor sequence, wherein said sequence, when presented in the context of the retrovirus-like particle is capable of generating an immune response specific to said antigenic anchor sequence when the particle is administered to a host.

2. The retrovirus-like particle of claim 1, wherein the archor sequence has between 5 and 100 amino acid residues.

3. The retrovirus-like particle of claim 2, wherein the anchor sequence has 10 about 75 amino acid residues.

4. The retrovirus-like particle of claim 2, wherein the anchor sequence comprises at least a portion of a transmembrane component of a membrane-spanning protein.

5. The retrovirus-like particle of claim 4, wherein the membrane spanning protein is a glycoprotein.

6. The retrovirus-like particle of claim 5, wherein the glycoprotein is an influenza virus protein.

7. The retrovirus-like particle of claim 6, wherein the influenza virus protein is a human influenza virus protein.

8. The retrovirus-like particle of claim 7, wherein the anchor sequence includes an amino acid sequence WILWISFAISCFLLCVVLLGFIMW (SEQ ID No: 2) or a portion, variation or mutant thereof capable of eliciting antibodies that recognize the sequence WILWISFAISCFLLCVVLLGFIMW (SEQ ID No: 2).

9. The retrovirus-like particle of claim 6, wherein the influenza virus protein is an avian influenza virus protein.

10. The retrovirus-like particle of claim 9, wherein the anchor sequence includes an amino acid sequence STVASSLALAIMIAGLSFWMCSNGSLQ (SEQ ID No: 3) or a portion, variation or mutant thereof capable of eliciting antibodies that recognize the sequence STVASSLALAIMIAGLSFWMCSNGSLQ (SEQ ID No: 3).

11. The retrovirus-like particle of claim 1, wherein said anchor sequence is inserted into the env gene product adjacent to and upstream of functional cleavage sites of the env gene product.

12. The retrovirus-like particle of claim 11, wherein said anchor sequence is inserted between amino acid residues 507 and 508 of the **HIV-1_{LAI}** env gene product, or the corresponding location in other **HIV** env gene products.

13. The retrovirus-like particle of claim 1, wherein the anchor seauence includes an amino acid sequence WILWISFAISCFLLCVVCWGSSCGPAKKATLGATFAFDSK EEWCREKKEQWE (SEQ ID No: 4) or a portion, variation or mutant thereof capable of eliciting antibodies that recognize the sequence WILWISFAISCFLLCVVCWGSSCGPAKKATLGATFAFDSKEEWCREKKEQWE (SEQ ID No: 4).

14. An immunogenic composition comprising the retrovirus-like particle of claim 1, wherein said composition is capable of eliciting a retroviral-specific immune response and an anchor sequence-specific immune response.

15. The immunogenic composition of claim 14, formulated for **mucosal** or parenteral administration.

16. The immunogenic composition of claim 14, formulated for oral, anal, vaginal, or intranasal administration.

17. The immunogenic composition of claim 15, further comprising at least one other immunogenic or immunostimulating material.

18. The composition of claim 17, wherein the at least one other immunostimulating material is an adjuvant.

19. The composition of claim 18, wherein the adjuvant is selected from the group consisting of aluminum phosphate, aluminum hydroxide, Freunds's incomplete adjuvant, and QS21.

20. A method of immunizing a host to produce a retroviral-specific immune response and an anchor sequence-specific immune response, comprising administering to the host the immunogenic composition of claim 14.

21. A non-infectious, non-replicating, **HIV** retrovirus-like particle containing a heterologous antigenic anchor sequence, comprising an assembly of: (a) a gag gene product; (b) a pol gene product; and (c) a modified env gene product comprising a non-retroviral, heterologous, antigenic, anchor sequence, wherein said anchor sequence replaces the endogenous anchoring functions of the env gene product; wherein said heterologous antigenic anchor sequence includes an amino acid sequence

selected from the group consisting of (I) WILWISFAISCFLLCVVLLGFIMW (SEQ ID NO: 2), (ii) STVASSLALAIMIAGLSFWMCSNGSLQ (SEQ ID NO: 3), and (iii) WILWISFAISCFLLCVVCWGSSCGPAKKATLGATFAFDSKEEWCREKKEQWE (SEQ ID NO: 4), and wherein said antigenic anchor sequence is inserted between amino acid residues 507 and 508 of the env gene product of the **HIV**-1 LAI isolate, and wherein said particle is encoded by a modified **HIV** genome deficient in long terminal repeats (LTRs) and containing the gag, pol, and env genes in their natural genomic arrangement and a heterologous nucleic acid insert encoding said heterologous antigenic anchor sequence, wherein said sequence, when presented in the context of the retrovirus-like particle is capable of generating an immune response specific to said antigenic anchor sequence when the particle is administered to a host.

L10 ANSWER 12 OF 22 USPATFULL on STN
1999:27618 Method for introducing and expressing genes in animal cells and live invasive bacterial vectors for use in the same.
Powell, Robert J., Baltimore, MD, United States
Lewis, George K., Baltimore, MD, United States
Hone, David M., Ellicott City, MD, United States
University of Maryland at Baltimore, Baltimore, MD, United States (U.S. corporation)
US 5877159 19990302
APPLICATION: US 1995-433790 19950503 (8) <--
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A method for introducing and expressing a gene in animal cells comprising infecting said animal cells with live invasive bacteria, wherein said bacteria contain a eukaryotic expression cassette encoding said gene, wherein said gene encodes a vaccine antigen, wherein said vaccine antigen is expressed at detectable levels, and wherein said animals cells are cultured in vitro.

2. The method of claim 1, wherein said animal cell is a mammalin cell.

3. The method of claim 2, wherein said mammalian cell is selected from the group consisting of human, bovine, ovine, porcine, feline, buffalo, canine, goat, equine, donkey, deer, and primate cells.

4. The method of claim 3, wherein said mammalian cell is human cells.

5. The method of claim 1, wherein said invasive bacteria is selected from the group consisting of Shigella spp, Listeria spp., Rickettsia spp and enteroinvasive Escherichia coli.

6. The method of claim 5, wherein said invasive bacteria is attenuated.

7. The method of claim 1, wherein said invasive bacteria is selected from the group consisting of Yersinia spp., Escherichia spp., Klebsiella spp., Bordetella spp., Neisseria spp., Aeromonas spp., Franciesella spp., Corynebacterium spp., Citrobacter spp., Chlamydia spp., Hemophilus spp., Brucella spp., Mycobacterium spp., Legionella spp., Rhodococcus spp., Pseudomonas spp., Helicobacter spp., Salmonella spp., Vibrio spp., Bacillus spp., Leishmania spp. and Erysipelothrix spp. which have been genetically engineered to mimic the invasion properties of Shigella spp., Listeria spp., Rickettsia spp., or enteroinvasive E. coli spp.

8. The method of claim 7, wherein said invasive bacteria is attenuated.

9. The method of claim 1, wherein said animal cells are infected with about 10^3 to 10^{11} viable invasive bacteria.

10. The method of claim 9, wherein said animal cells are infected with about 10^5 to 10^9 viable invasive bacteria.

11. The method of claim 1, wherein said animal cells are infected at a multiplicity of infection ranging from about 0.1 to 10^6.

12. The method of claim 11, wherein said animal cells are infected at a multiplicity of infection ranging from about 10^2 to 10^4.

13. A method for introducing and expressing a gene in animal cells comprising infecting said animal cells with live invasive Shigella spp., wherein said Shigella spp. contain a eukaryotic expression cassette encoding said gene, wherein said gene encodes a vaccine antigen, wherein said vaccine antigen is expressed at detectable levels, and wherein said animals cells are cultured in vitro.

14. The method of claim 1, wherein said Shigella spp is Shigella flexneri.

15. A method for inducing an immune response in an animal comprising infecting said animal with attenuated live invasive bacteria, wherein said bacteria contain a eukaryotic expression cassette encoding said gene, wherein said gene encodes a vaccine antigen, wherein said vaccine antigen is expressed at levels sufficient to induce an immune response, wherein said invasive bacteria are administered to a **mucosal** surface of said animal.

16. The method of claim 13, wherein said invasive bacteria are intranasally administered to said animal.

17. The method of claim 15, wherein said animal is a human.

18. The method of claim 15, wherein said attenuated bacteria is attenuated Shigella spp. or attenuated Salmonella spp.

19. The method of claim 16, wherein said animal is a mammal.

20. The method of claim 17, wherein said invasive bacteria are intranasally administered to said human.

21. The method of claim 19, wherein said invasive bacteria are intranasally administered to said mammal.

22. The method of claim 18, wherein said attenuated bacteria is attenuated Shigella spp. is Shigella flexneri.

23. The method of claim 15, wherein said invasive bacteria is selected from the group consisting of Shigella spp, Listeria spp., Rickettsia spp and enteroinvasive Escherichia coli.

24. The method of claim 15, wherein said invasive bacteria is selected from the group consisting of Yersinia spp., Escherichia spp., Klebsiella spp., Bordetella spp., Neisseria spp., Aeromonas spp., Franciesella spp., Corynebacterium spp., Citrobacter spp., Chlamydia spp., Hemophilus spp., Brucella spp., Mycobacterium spp., Legionella spp., Rhodococcus spp., Pseudomonas spp., Helicobacter spp., Salmonella spp., Vibrio spp., Bacillus spp., Leishmania spp. and Erysipelothrix spp. which have been genetically engineered to mimic the invasion properties of Shigella spp., Listeria spp., Rickettsia spp., or enteroinvasive E. coli spp.

L10 ANSWER 13 OF 22 USPATFULL on STN
1999:21889 Reduction of false positives in oral-fluid based immunoassays.
Thieme, Thomas, Independence, OR, United States
Klimkow, Nanette, Beaverton, OR, United States
Epitope, Inc., Beaverton, OR, United States (U.S. corporation)
US 5871905 19990216
APPLICATION: US 1996-707446 19960904 (8) <--
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A method of reducing false positives in assays for the detection of an analyte in an oral fluid sample, said method comprising the step of providing an oral fluid sample combined with a bile acid bile or salt; wherein said bile acid bile or salt is present in a concentration sufficient to reduce the rate of occurrence of false positives in said assays; and wherein said assays are characterized by the use of a particulate moiety as a detectable label.

2. The method of claim 1, wherein said bile acid bile or salt is selected from the group consisting of deoxycholic acid (deoxycholate salt), cholic acid (cholate salt), chenodeoxycholic acid (chenodeoxycholate salt), glycodeoxycholic acid (glycodceoxycholate salt), and taurodeoxycholic acid (taurodeoxycholate salt).

3. The method of claim 2, wherein said bile acid or bile salt is deoxycholic acid or deoxycholate salt.

4. The method of claim 1, wherein said bile acid or bile salt ranges in concentration from about 0.1 weight percent to about 1.0 weight percent of the oral fluid/bile salt or bile acid combination.

5. The method of claim 1, further comprising contacting a chelator of divalent cations with said oral fluid sample.

6. The method of claim 5, wherein said chelator is selected from the group consisting of EDTA, EGTA, NTA, CDTA, sodium citrate, and a chelating resin.

7. The method of claim 6, wherein said chelator is EDTA.

8. The method of claim 1, wherein said assay is an immunoassay that use a particulate detectable label.

9. The method of claim 8, wherein said assay is an immunochromatography assay.

10. The method of claim 1, wherein said providing comprises using a collection means selected from the group consisting of a sponge, an absorbent pad, a salt-impregnated absorbent pad, an aspirator, and a mouth rinse to collect said oral fluid sample.

11. The method of claim 1, wherein said oral fluid sample is predominantly **mucosal** transudate.

12. The method of claim 1, wherein said analytes are selected from the group consisting of antibodies to antigens of infectious diseases, antigens of infections diseases, hormones, growth factors, therapeutic drugs, drugs of abuse and products of the metabolism of drugs of abuse.

13. The method of claim 12, wherein said antigens are antigens of hepatitis B and said antibodies are selected from the group consisting of antibodies to **HIV**, antibodies to HTLV, antibodies to Helicobacter pylon, antibodies to hepatitis, antibodies to measles, antibodies to mumps, and antibodies to rubella.

14. The method of claim 13, wherein said analyte is an antibody to **HIV**.

15. The method of claim 12, wherein said therapeutic drugs and drugs of abuse or products of the metabolism of drugs of abuse are selected from the group consisting of tetrahydrocannabinol, nicotine, ethanol, theophylline, phenytoin, acetaminophen, lithium, diazepam, nortryptyline, secobarbital, phenobarbitol.

16. The method of claim 12, wherein said hormones are selected from the group consisting of testosterone, estradiol, 17-hydroxyprogesterone, progesterone, thyroxine, thyroid stimulating hormone, follicle stimulating hormone, and luteinizing hormone.

17. The method of claim 1, wherein said method further comprises contacting said oral fluid sample with a chelator of divalent cations and said oral fluid sample is assayed in a lateral flow immunochromatography assay.

18. The method of claim 17, wherein said bile salt or bile acid is deoxycholic acid or deoxycholate salt; said chelator is EDTA.

L10 ANSWER 14 OF 22 USPATFULL on STN
1999:15678 Nucleic acids encoding for non-infectious, replication-defective, self-assembling **HIV**-1 viral particles containing antigenic markers in the gag coding region.
Rovinski, Benjamin, Thornhill, Canada
Cao, Shi-Xian, Etobicoke, Canada
Yao, Fei-Long, North York, Canada
Persson, Roy, North York, Canada
Klein, Michel H., Willowdale, Canada
Connaught Laboratories Limited, North York, Canada (non-U.S. corporation)
US 5866320 19990202
APPLICATION: US 1995-470419 19950606 (8) <--
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A nucleic acid molecule encoding a non-infectious, replication-deficient, retrovirus-like particle containing a heterologous antigenic marker, comprising: a modified **HIV** genome, deficient in long terminal repeats (LTRs), containing gag, pol and env genes in their natural genomic arrangement and a heterologous nucleic acid insert encoding at least one non-retroviral, non-mammalian antigenic marker wherein said marker, when presented in the context of the retrovirus-like particle, capable of generating an immune response specific to said marker when the encoded particle is administered to a host.

2. The nucleic acid molecule of claim 1, wherein the segment encoding the at least one antigenic marker contains between 15 and 300 nucleotides.

3. The nucleic acid molecule of claim 2, wherein the segment encoding the at least one antigenic marker contains between 30 to 225 nucleotides.

4. The nucleic acid molecule of claim 2, wherein the segment encoding the at least one antigenic marker encodes at least one antigenic epitope from tobacco mosaic virus coat protein.

5. The nucleic acid molecule of claim 4 wherein the at least one antigenic epitope from tobacco mosaic virus coat protein includes an amino acid sequence AFDTRNRIIEVEN (SEQ ID NO: 1) or a portion, variation or mutant thereof capable of eliciting antibodies that recognize the sequence AFDTRNRIIEVEN (SEQ ID NO:1).

6. The nucleic acid molecule of claim 1, wherein the segment encoding the at least one antigenic marker is contained within the gag gene to provide a modified gag gene encoding a hybrid war gene product having the particle-forming characteristics of unmodified gag gene product.

7. The nucleic acid molecule of claim 6, wherein the segment encoding the at least one antigenic marker is inserted into the gag gene to provide the antigenic marker at an antigenically-active insertion site in the hybrid gag gene product.

8. The nucleic acid molecule of claim 7 wherein the segment encoding the at least one antigenic marker is inserted at an insertion site, located at the PstI site at nucleotide 1415 of the gag gene of **HIV**-1 LAI isolate or the corresponding location of other retroviral gag genes.

9. A nucleic acid molecule encoding a non-infectious, replication-deficient, **HIV** retrovirus-like particle containing a heterologous antigenic marker, comprising: a modified **HIV** retroviral genome deficient in long terminal repeats (LTRs) and containing gag, pol and env genes in their natural genomic arrangement and a heterologous nucleic acid insert encoding at least one non-retroviral non-mammalian antigenic marker wherein said modified genome comprises from one to four copies of a nucleic acid sequence selected from the group consisting of: (a) 5' GCATTCGACACTAGAAATAGAATAATAGAAGTTGAAAAT 3' (SEQ ID NO: 5); or (b) 3'CGTAAGCTGTGATCTTTATCTTATTATCTTCAACTTTTA5' (SEQ. ID NO: 6);, and said marker is inserted into the PstI site at nucleotide 1415 of the **HIV**-1_{LAI} gag gene, which when presented in the context of the retrovirus-like particles, is capable of encoded particle is administered to a host.

10. An immunogenic composition capable of eliciting a retroviral specific immune response and a specific immune response against a non-retroviral marker, comprising the nucleic acid molecule of claim 1 and a carrier therefor.

11. The immunogenic composition of claim 10 formulated for **mucosal** or parenteral administration.

12. The immunogenic composition of claim 10 formulated for oral, anal, vaginal, or intranasal administration.

13. The immunogenic composition of claim 11 further comprising at least one other immunogenic or immunostimulating material.

14. The composition of claim 13 wherein the at least one other immunostimulating material is an adjuvant.

15. The composition of claim 14, wherein the adjuvant is selected from the group consisting of aluminum phosphate, aluminum hydroxide, Freund's incomplete adjuvant, and QS21.

16. A method of immunizing a host to produce a retroviral specific immune response and a specific immune response against the antigenic marker, comprising administering to the host an immunoeffective amount of the immunogenic composition of claim 10.

17. A method of identifying antiserum generated by immunization with the immunogenic composition of claim 10, comprising: detecting antibodies specific for said antigenic marker in said antiserum.

L10 ANSWER 15 OF 22 USPATFULL on STN
1998:127915 Vaccine compositions and method for induction of **mucosal** immune response via systemic vaccination.
Daynes, Raymond A., Park City, UT, United States
Araneo, Barbara A., Salt Lake City, UT, United States
University of Utah Research Foundation, Salt Lake City, UT, United States (U.S. corporation)
US 5824313 19981020
APPLICATION: US 1995-480567 19950607 (8) <--
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A method for inducing an antigen-specific **mucosal** immune response in a vertebrate animal, comprising administering an effective amount of a lymphoid organ modifying agent selected form the group consisting of 1,25-dihydroxy-16-ene Vitamin D_3 and calcipotriene to the vertebrate animal at a peripheral, non-**mucosal** site which drains into a peripheral lymphoid organ or compartment, and administering an effective amount of a specific antigen to the vertebrate animal at a peripheral, non-**mucosal** site which drains into said peripheral lymphoid organ or compartment.

2. The method of claim 1 wherein said lymphoid organ modifying agent is administered intramuscularly.

3. The method of claim 1 wherein said lymphoid organ modifying agent is administered intradermally.

4. The method of claim 1 wherein said lymphoid organ modifying agent is administered subcutaneously.

5. The method of claim 1 wherein said effective amount of said lymphoid organ modifying agent is 0.01-5.0 μg/kg body weight.

6. The method of claim 1 wherein said effective amount of said lymphoid organ modifying agent is in the range of 0.1-500 μg.

7. The method of claim 1 wherein said lymphoid organ modifying agent administering step commences at a time up to 24 hours earlier than the time said specific antigen administering step commences.

8. The method of claim 1 wherein said lymphoid organ modifying agent administering step commences at about the same time as said specific antigen administering step commences.

9. The method of claim 1 wherein said lymphoid organ modifying agent administering step commences at a time up to 6 days later than the time said specific antigen administering step commences.

10. The method of claim 1 wherein said lymphoid organ modifying agent administering step and said specific antigen administering step are carried out at least partly concurrently.

11. The method of claim 1 wherein said specific antigen and said lymphoid organ modifying agent are combined prior to said administering steps.

12. The method of claim 1 which further comprises administering an effective amount of a dehydroepiandrosterone (DHEA) congener.

13. The method of claim 12 wherein said DHEA congener has the formula ##STR2## wherein X is H or halogen; R^1, R^2 and R^3 are independently .dbd.O, --OH, --SH, H, halogen, pharmaceutically acceptable ester, pharmaceutically acceptable thioester, pharmaceutically acceptable ether, pharmaceutically acceptable thioether, pharmaceutically acceptable inorganic esters, pharmaceutically acceptable monosaccharide, disaccharide or oligosaccharide, spirooxirane, spirothirane, $--OSO_2$ R^5 or $--OPOR^5$ R^6 ; R^5 and R^6 are independently --OH, pharmaceutically acceptable esters or pharmaceutically acceptable ethers; and pharmaceutically acceptable salts.

14. The method of claim 12 wherein said effective amount of DHEA congener is 10-1,000 μg when administration is by injection, or 10-100 mg/day when administration is oral.

15. The method of claim 12 wherein said DHEA congener is administered

separately from said lymphoid organ modifying agent.

16. The method of claim 15 wherein said DHEA congener is administered up to 14 days prior to said lymphoid organ modifying agent.

17. The method of claim 12 wherein said DHEA congener is administered concurrently with said lymphoid organ modifying agent.

18. The method of claim 12 wherein said DHEA congener is administered separately from said lymphoid organ modifying agent and said antigen.

19. The method of claim 18 wherein said DHEA congener is administered up to 14 days prior to said lymphoid organ modifying agent and said antigen.

20. The method of claim 18 wherein said DHEA congener is administered up to 6 hours after said lymphoid organ modifying agent derivative and said antigen.

21. The method of claim 12 wherein said antigen, lymphoid organ modifying agent and said DHEA congener are combined prior to administration.

22. A method for inducing production of antigen-specific antibodies in the mammary secretions of a female mammal, comprising treating the female mammal according to the method of claim 1.

23. A method for inducing production of antigen-specific antibodies in the mammary secretions of a female mammal, comprising treating the female mammal according to the method of claim 12.

24. A method for conferring a specific passive immunity to a suckling mammal, comprising permitting the suckling mammal to consume mammary secretions from a female mammal treated according to the method of claim 1.

25. A method for conferring a specific passive immunity to a suckling mammal, comprising permitting the suckling mammal to consume mammary secretions from a female mammal treated according to the method of claim 12.

26. A method for inducing an antigen-specific **mucosal** immune response in a vertebrate animal, which comprises administering an effective amount of at least one lymphoid organ modifying agent selected from the group of $1,25(OH)_2\ D_3$ or all trans-retinoic acid to the vertebrate animal at a peripheral, non-**mucosal** site which drains into a peripheral lymphoid organ or compartment, administering an effective amount of a dehydroepiandrosterone (DHEA) congener to the vertebrate animal and administering an effective amount of a specific antigen to the vertebrate animal at a peripheral, non-**mucosal** site which drains into said peripheral lymphoid organ or compartment.

27. The method of claim 26 wherein said lymphoid organ modifying agent is $1,25(OH)_2\ D_3$.

28. The method of claim 26 wherein said lymphoid organ modifying agent is all trans-retinoic acid.

29. The method of claim 26 wherein said lymphoid organ modifying agent is administered intramuscularly.

30. The method of claim 26 wherein said lymphoid organ modifying agent is administered intradermally.

31. The method of claim 26 wherein said lymphoid organ modifying agent is administered subcutaneously.

32. The method of claim 26 wherein said effective amount of said lymphoid organ modifying agent is 0.01-5.0 μg/kg body weight.

33. The method of claim 26 wherein said effective amount of said lymphoid organ modifying agent is in the range of 0.1-500 μg.

34. The method of claim 26 wherein said lymphoid organ modifying agent administering step, said specific antigen administering step and said DHEA congener administering step are carried out at least partly concurrently.

35. The method of claim 26 wherein said specific antigen, said lymphoid

organ modifying agent and said DHEA congener are combined prior to said administering steps.

36. The method of claim 26 wherein said DHEA congener has the formula ##STR3## wherein X is H or halogen; R^1, R^2 and R^3 are independently .dbd.O, --OH, --SH, H, halogen, pharmaceutically acceptable ester, pharmaceutically acceptable thioester, pharmaceutically acceptable ether, pharmaceutically acceptable thioether, pharmaceutically acceptable inorganic esters, pharmaceutically acceptable monosaccharide, disaccharide or oligosaccharide, spirooxirane, spirothirane, $--OSO_2 R^5$ or $--OPOR^5 R^6$; R^5 and R^6 are independently --OH, pharmaceutically acceptable esters or pharmaceutically acceptable ethers; and pharmaceutically acceptable salts, with the proviso that when R^2 is .dbd.O, R^3 is H, and X is H or halogen, then R^1 is not --OH, --SH, $--OSO_2 R^5$ or $--OPOR^5 R^6$, where R^5 and R^6 are independently a straight or branched C_{1-14} alkyl.

37. The method of claim 26 wherein said effective amount of DHEA congener is 10-1,000 μg when administration is by injection, or 10-100 mg/day when administration is oral.

38. The method of claim 36 wherein said lymphoid organ modifying agent is $1,25(OH)_2 D_3$.

39. The method of claim 36 wherein said lymphoid organ modifying agent is all trans-retinoic acid.

40. The method of claim 26 wherein said DHEA congener is administered separately from said lymphoid organ modifying agent.

41. The method of claim 40 wherein said DHEA congener is administered up to 14 days prior to said lymphoid organ modifying agent.

42. The method of claim 26 wherein said DHEA congener is administered concurrently with said lymphoid organ modifying agent.

43. The method of claim 26 wherein said DHEA congener is administered separately from said lymphoid organ modifying agent and said antigen.

44. The method of claim 43 wherein said DHEA congener is administered up to 14 days prior to said lymphoid organ modifying agent and said antigen.

45. The method of claim 43 wherein said DHEA congener is administered up to 6 hours days after said lymphoid organ modifying agent and said antigen.

46. The method of claim 26 wherein said antigen, lymphoid organ modifying agent and said DHEA congener are combined prior to administration.

47. A method for inducing production of antigen-specific antibodies in the mammary secretions of a female mammal, comprising treating the female mammal according to the method of claim 26.

48. A method for conferring a specific passive immunity to a suckling mammal, comprising permitting the suckling mammal to consume mammary secretions from a female mammal treated according to the method of claim 26.

49. A vaccine composition comprising an effective amount of a lymphoid organ modifying agent selected form the group consisting of 1,25-dihydroxy-16-ene Vitamin D_3 and calcipotriene and an effective amount of a specific antigen in a pharmaceutically acceptable carrier to induce an antigen-specific **mucosal** immune response.

50. The vaccine composition of claim 49 which further comprises an effective amount of a dehydroepiandrosterone (DHEA) congener to enhance an antigen-specific immune response.

51. The vaccine composition of claim 50 wherein said DHEA congener has the formula ##STR4## wherein X is H or halogen; R^1, R^2 and R^3 are independently .dbd.O, --OH, --SH, H, halogen, pharmaceutically acceptable ester, pharmaceutically acceptable thioester, pharmaceutically acceptable ether, pharmaceutically acceptable thioether, pharmaceutically acceptable inorganic esters, pharmaceutically acceptable monosaccharide, disaccharide or

oligosaccharide, spirooxirane, spirothirane, --OSO_2 R^5 or --$OPOR^5$ R^6 ; R^5 and R^6 are independently --OH, pharmaceutically acceptable esters or pharmaceutically acceptable ethers; and pharmaceutically acceptable salts.

52. The vaccine composition of claim 49 wherein said antigen is capable of eliciting an immune response against viral hepatitis, influenza, diphtheria, tetanus, pertussis, measles, mumps, rubella, polio, pneumococcus, herpes, respiratory syncytial virus, haemophilus influenza type b, varicella-zoster virus or rabies.

53. The vaccine composition of claim 50 wherein said antigen is capable of eliciting an immune response against viral hepatitis, influenza, diphtheria, tetanus, pertussis, measles, mumps, rubella, polio, pneumococcus, herpes, respiratory syncytial virus, haemophilus influenza type b, varicella-zoster virus or rabies.

54. A vaccine composition comprising an effective amount of at least one lymphoid organ modifying agent selected from the group consisting of 1,25-dihydroxy Vitamin D_3 ($1,25(OH)_2$ D_3) and all trans-retinoic acid, an effective amount of a dehydroepiandrosterone (DHEA) congener, and effective amount of a specific antigen in a pharmaceutically acceptable carrier to induce an antigen-specific **mucosal** immune response.

55. The vaccine composition of claim 54 wherein said lymphoid organ modifying agent is $1,25(OH)_2$ D_3.

56. The vaccine composition of claim 54 wherein said lymphoid organ modifying agent is all trans-retinoic acid.

57. The vaccine composition of claim 54 wherein said DHEA congener has the formula ##STR5## wherein X is H or halogen; R^1, R^2 and R^3 are independently .dbd.O, --OH, --SH, H, halogen, pharmaceutically acceptable ester, pharmaceutically acceptable thioester, pharmaceutically acceptable ether, pharmaceutically acceptable thioether, pharmaceutically acceptable inorganic esters, pharmaceutically acceptable monosaccharide, disaccharide or oligosaccharide, spirooxirane, spirothirane, --OSO_2 R^5 or --$OPOR^5$ R^6 ; R^5 and R^6 are independently --OH, pharmaceutically acceptable esters or pharmaceutically acceptable ethers; and pharmaceutically acceptable salts, with the proviso that when R^2 is .dbd.O, R^3 is H, and X is H or halogen, then R^1 is not --OH, --SH, --OSO_2 R^5 or --$OPOR^5$ R^6, where R^5 and R^6 are independently a straight or branched C_{1-14} alkyl.

58. The vaccine composition of claim 57 wherein said lymphoid organ modifying agent is $1,25(OH)_2$ D_3.

59. The vaccine composition of claim 57 wherein said lymphoid organ modifying agent is all trans-retinoic acid.

60. The vaccine composition of claim 54 wherein said antigen is capable of eliciting an immune response against viral hepatitis, influenza, diphtheria, tetanus, pertussis, measles, mumps, rubella, polio, pneumococcus, herpes, respiratory syncytial virus, haemophilus influenza type b, varicella-zoster virus or rabies.

61. The vaccine composition of claim 57 wherein said antigen is capable of eliciting an immune response against viral hepatitis, influenza, diphtheria, tetanus, pertussis, measles, mumps, rubella, polio, pneumococcus, herpes, respiratory syncytial virus, haemophilus influenza type b, varicella-zoster virus or rabies.

L10 ANSWER 16 OF 22 USPATFULL on STN
1998:88827 Uses of aloe products in the treatment of chronic respiratory diseases.
Carpenter, Robert H., Bastrop, TX, United States
McDaniel, Harley R., Dallas, TX, United States
McAnalley, Bill H., Grand Prairie, TX, United States
Carrington Laboratories, Inc., Irving, TX, United States (U.S. corporation)
US 5786342 19980728
APPLICATION: US 1995-462821 19950605 (8) <--
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A method for reducing symptoms associated with chronic respiratory

diseases in an animal, comprising: administering to said animal an amount of acetylated mannan compound sufficient to reduce itching, burning, congestion, watering of **mucosal** membranes, sinus headaches produced by swollen nasal mucosa, wheezing, coughing, bronchitis, tightness in the chest, and difficulty breathing in said animal.

2. The method according to claim 1 wherein said acetylated mannan compound comprises acemannan.

3. The method according to claim 1, wherein said animal is a human.

L10 ANSWER 17 OF 22 USPATFULL on STN
1998:64760 Vaccines against intracellular pathogens using antigens encapsulated within biodegradble-biocompatible microspheres.
Burnett, Paul R., Silver Spring, MD, United States
Van Hamont, John E., Ft. Meade, MD, United States
Reid, Robert H., Kensington, MD, United States
Setterstrom, Jean A., Alpharetta, GA, United States
Van Cott, Thomas C., Brookeville, MD, United States
Birx, Debrah L., Potomac, MD, United States
The United States of America as represented by the Secretary of the Army, Washington, DC, United States (U.S. government)
US 5762965 19980609
APPLICATION: US 1996-598874 19960209 (8) <--
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. An immunostimulating composition comprising encapsulating microspheres comprised of (a) a biodegradable-biocompatible poly(DL-lactide-co-glycolideas the bulk matrix produced by a solvent evaporation process wherein the molecular weight of the copolymer is between 4,000 to 100,000 daltons and (b) an immunogenic substance consisting of a conformationally native subunit of chronic intracellular pathogen which, in the course of natural infection with that pathogen, is exposed to the host immune system on the surface of free pathogen and/or pathogen-infected cells.

2. The immunostimulating composition described in claim 1 wherein the antigen is pre-encapsulated into a conformationally stabilizing hydrophilic matrix consisting of an appropriate mono, di- or tri-saccharide or other carbohydrate susbstance by lyophilization prior to its final encapsulation into the PLG microsphere by a solvent extraction process employing acetonitrile as the polymer solvent, mineral oil as the emulsion's external phase, and heptane as the extractant.

3. The immunostimulating compositions described in claims 1 or 2 wherein the immunogenic substance is a native (oligomeric)**HIV**-1 envelope antigen that is conformationally stabilized by the polymer matrix and serves to elicit in animals the production of **HIV** specific cytotoxic T lumphocytes and antibodies preferentially reactive against native **HIV**-1 envelope antigen.

4. The immunostimulating compositions described in claim 3 wherein the amount of said immunogenic substance within the microcapsule comprises between 0.5% to 5.0% of the weight of said composition.

5. The immunostimulating compositions describe in claim 4 wherein the relative ratio between the amount of the lactide:glycolide components of said matrix is within the range of 52:48 to 0:100.

6. The immunostimulating compositions described in claim 5 wherein the molecular weight of said copolymer is between 4,000 to 50,000 daltons.

7. A vaccine consisting of a blend of the immunostimulating compositions described in claims 5 or 6.

8. The immunostimulating compositions described in claim 5, employed as a parentally administered vaccine wherein the diameter size range of said vaccine microspheres lies between 1 nanometer and 20 microns.

9. The immunostimulating compositions described in claim 5, employed as a **mucosal** vaccine wherein the size of more than 50% (by volume) of said vaccine microspheres is between 5 to 10 microns in diameter.

10. A composition in accordance with claim 1 wherein the microspheres further contain a pharmaceutically-acceptable adjuvant.

11. A vaccine consisting of a blend of the immunostimulating compositions described in claims 5 or 6.

12. The immunostimulating compositions described in claim 6 employed as a parentally administered vaccine wherein the diameter size range of said vaccine microspheres lies between 1 nanometer and 20 microns.

13. The immunostimulating compositions described in claim 7 employed as a parentally administered vaccine wherein the diameter size range of said vaccine microspheres lies between 1 nanometer and 20 microns.

14. The immunostimulating compositions described in claim 6 employed as a **mucosal** vaccine wherein the size of more than 50% (by volume) of said vaccine microspheres is between 5 to 10 microns in diameter.

L10 ANSWER 18 OF 22 USPATFULL on STN
1998:33575 Protection from viral infection via colonization of **mucosal** membranes with genetically modified bacteria.
Lee, Peter Poon-Hang, 1130 Welch Rd., Apt. 313, Palo Alto, CA, United States 94304
US 5733540 19980331
APPLICATION: US 1995-401070 19950308 (8) <--
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A method of binding viral particles to non-host cells in a host to increase the minimum viral load necessary to infect the host said method comprising contacting a **mucosal** surface of the host with an amount of transformed bacteria sufficient to colonize the **mucosal** surface, said bacteria having been transformed with genetic material so as to confer upon the bacteria the capacity to bind the viral particles.

2. A method of claim 1 where the transformed bacteria expresses a polypeptide on its surface which serves as the host receptor for the virus.

3. A method of claim 2 where the bacteria are transformed with genetic material which directs surface expression of a protein with comprising an ICAM-1 domain, where the virus is a human rhinovirus, and the host is human.

4. A method of claim 2 where the bacteria are transformed with genetic material which directs surface expression of a protein with a CD4 receptor, the virus is a **human immunodeficiency virus**, and the host is human.

5. A method of claim 2 where the bacteria are transformed with genetic material which directs surface expression of a protein with a poliovirus receptor, the virus is a poliovirus, and the host is human.

6. A method of claim 2 where the bacteria are transformed with genetic material which directs surface expression of a protein with a human complement receptor 2, the virus is an "epstein-barr" virus, and the host is human.

7. A method of claim 1 where the transformed bacteria expresses on its surface an antibody fragment against a conserved determinant on the virus.

8. A method of claim 7 where the bacteria are transformed with genetic material which directs surface expression of an antibody fragment against a monomorphic determinant of the human HLA DR molecule, the virus is a **human immunodeficiency virus**, and the host is human.

9. A method of claim 7 where the bacteria are transformed with genetic material which directs surface expression of an antibody fragment against a conserved determinant on the rotavirus coat protein, the virus is a rotavirus, and the host is human.

10. A method of claim 7 where the bacteria are transformed with genetic material which directs surface expression of an antibody fragment against a conserved determinant on the herpes simplex virus coat protein, the virus is a herpes simplex virus, and the host is human.

11. A method of claim 7 where the bacteria are transformed with genetic material which directs surface expression of an antibody fragment against a conserved determinant on the human papilloma virus coat protein, the virus is a human papilloma virus, and the host is human.

12. A method of claim 7 where the bacteria are transformed with genetic material which directs surface expression of an antibody fragment against a conserved determinant on the adenovirus coat protein, the virus is an adenovirus, and the host is human.

13. A method of claim 7 where the bacteria are transformed with genetic material which directs surface expression of an antibody fragment against a conserved determinant on the respiratory syncytia virus coat protein, the virus is a respiratory syncytia virus, and the host is human.

14. A method of claim 7 where the bacteria are transformed with genetic material which directs surface expression of an antibody fragment against a conserved determinant on the corona virus coat protein, the virus is a corona virus, and the host is human.

15. A method of claim 7 where the bacteria are transformed with genetic material which directs surface expression of an antibody fragment against a conserved determinant on the capsids of a virus selected from the group consisting of: cytomegalovirus, coxsackievirus, echovirus, hepatitis A virus and parainfluenza virus.

16. A method of claim 1 wherein the bacteria has a cell membrane and the virus has an envelope, wherein the transformed bacteria causes fusion between its cell membrane and the envelope of the virus.

17. A method of claim 16 wherein the transformed bacteria fuses with bound viral particles through a fusogenic domain engineered into the virus-binding polypeptide.

18. A method of claim 1 wherein the transformed bacteria is conferred sufficient selective advantage over other resident bacteria to allow said transformed bacteria to successfully colonize and survive indefinitely on a selected **mucosal** surface.

19. A method of claim 18 wherein the transformed bacteria is conferred enhanced ability to adhere to a host **mucosal** surface through a domain in the heterologous protein which binds to a determinant on a selected **mucosal** surface.

20. A method of claim 1 where the **mucosal** surface is the nasopharynx, oropharynx, esophagus, small intestines, large intestines, rectum, vagina, or penis.

21. A method of claim 1 where the transformed bacteria is resistant to an antibiotic and is co-administered with said antibiotic to enhance colonization of the transformed bacteria.

22. A method of claim 1 where the transformed bacteria is co-administered with an enzyme which degrades the **mucosal** surface to enhance colonization of the transformed bacteria.

23. A method of claim 22 wherein the enzyme is DNAse, peptidase, collagenase, hyaluronidase, or other carbohydrate degrading enzymes.

24. A method of claim 1 where transformed bacteria are applied to a **mucosal** surface through the use of a liquid solution, foam, suppository, sponge, or capsule.

25. A method of inhibiting an infection transmitted through vaginal intercourse by the application of transformed bacterial into the vaginal vault at the time of intercourse that binds and inactivates an infectious agent.

26. A method of claim 25 wherein the bacteria inactivate a pathogen selected from the group consisting of: **HIV**, HPV, HSV, gonorrhea, syphilis and chlamydia.

27. A method of claim 25 where the transformed bacteria are administered in the form of a vaginal foam or sponge, and may be administered in conjunction with other agents such as nonbacteriocidal spermicides.

28. A method of preventing the spread of a viral pathogen from an infected individual to others with transformed bacteria by administering an amount of bacteria sufficient to colonize the **mucosal** surfaces of the infected individual wherein said bacteria bind and inactivate infectious viral particles exiting the infected host.

L10 ANSWER 19 OF 22 USPATFULL on STN
1998:14497 Solid fat nanoemulsions as vaccine delivery vehicles.
Anselem, Shimon, Rehovot, Israel
Lowell, George H., Baltimore, MD, United States
Aviv, Haim, Rehovot, Israel
Friedman, Doron, Carmei Yosef, Israel
Pharmos Corporation, New York, NY, United States (U.S. corporation)The United States of America as represented by the Secretary of the Army, Washington, DC, United States (U.S. government)
US 5716637 19980210
WO 9426255 19941124
APPLICATION: US 1995-553350 19951116 (8) <--
WO 1994-US5589 19940518 19951116 PCT 371 date 19951116 PCT 102(e) date<--
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A pharmaceutical composition for the administration of antigen which comprises a nanoemulsion of a plurality of noncellular lipid particles having a mean diameter of about 10 to 250 nm, as determined on a weight basis, the particles being suspended in an aqueous continuous phase, wherein each said lipid particle comprises a lipid core composed of a lipid which is a solid or liquid crystal as determined in bulk at a temperature of about 25° C. or higher, and at least one phospholipid bilayer surrounding said core and encapsulating a portion of said aqueous continuous phase, said particles entrapping about 0.001 to 5% of an immunogen in said lipid core or in said encapsulated aqueous phase.

2. The pharmaceutical composition of claim 1 wherein the mean particle diameter of said lipid particles falls within the range of about 20 to 180 nm as determined on a weight basis.

3. The pharmaceutical composition of claim 2 wherein the particle diameter of at least 99% of said lipid particles falls within the range of about 50 to 150 nm as determined on a weight basis.

4. The pharmaceutical composition of claim 2 wherein the lipid core comprises a fatty acid ester.

5. The pharmaceutical composition of claim 4 wherein the lipid core has a solid to fluid phase transition temperature below 37° C. as determined in bulk.

6. The pharmaceutical composition of claim 4 wherein the lipid core comprises a triglyceride.

7. The pharmaceutical composition of claim 6 wherein said triglyceride comprises a fatty acid moiety of C_{10} to C_{18}.

8. The pharmaceutical composition of claim 6 wherein said triglyceride is completely saturated.

9. The pharmaceutical composition of claim 6 wherein said triglyceride is selected from the group consisting of tricaprin, trilaurin, trimyristin, tripalmitin, and tristearin.

10. The pharmaceutical composition of claim 6 wherein the mole ratio of phospholipid to total lipid is in the range of from 0.1:1 to 0.5:1.

11. The pharmaceutical composition of claim 6 wherein the weight ratio of phospholipid to triglyceride is in the range of from 0.5:1 to 1.5:1.

12. The pharmaceutical composition of claim 4 wherein said phospholipid is a phosphatidylcholine.

13. The pharmaceutical composition of claim 12 wherein said phosphatidylcholine is egg phosphatidylcholine.

14. The pharmaceutical composition of claim 12 wherein said phosphatidylcholine has a transition temperature below 25° C.

15. The pharmaceutical composition of claim 12 wherein said phosphatidylcholine is saturated.

16. The pharmaceutical composition of claim 1 wherein said lipid particle contains cholesterol or cholesteryl esters.

17. The composition of claim 1 wherein the immunogen is hydrophilic,

lipophilic, or amphophilic.

18. The composition of claim 1 wherein the immunogen is a peptide, protein, or glycoprotein.

19. The composition of claim 18 wherein the antigen is the **gp160** envelope protein of the **HIV** virus, or a fragment thereof.

20. The composition of claim 18 wherein the antigen is the surface glycoprotein of a Leishmania parasite, or a fragment thereof.

21. The composition of claim 20 wherein the surface glycoprotein or peptide is covalently conjugated to a hydrophobic component.

22. The composition of claim 21 wherein the hydrophobic component is lauryl-cysteine.

23. The composition of claim 1 wherein the immunogen is a protein toxoid.

24. The composition of claim 23 wherein the immunogen is Staphylococcus Enterotoxin B toxoid.

25. The composition of claim 1 wherein the immunogen is complexed with a proteosome.

26. The composition of claim 1 wherein the nanoemulsion further comprises a bioadhesive or mucoadhesive macromolecule.

27. The composition of claim 26 wherein the said mucoadhesive macromolecule is a polymer.

28. The composition of claim 26 wherein the said mucoadhesive macromolecule is selected from the group of acidic nonnatural polymers consisting of polymers and copolymers containing acrylic acid units, polymers and copolymers containing methacrylic acid units, and poly(methylvinylether/maleic anhydride) copolymer.

29. The composition of claim 28 wherein the said polymer is polyacrylic acid.

30. The composition of claim 1 which contains no added muramyl peptides.

31. The pharmaceutical composition of claim 1 wherein said lipid particle is substantially free of lipase and phospholipase activity.

32. A method for delivery of an immunogen to an animal, comprising administering to said animal a pharmaceutical according to claim 1.

33. The method of claim 32 wherein the mean diameter of the lipid particles in said composition is in the range of about 20 to 180 nm.

34. The method of claim 32 wherein said composition is administered parenterally, orally, intranasally, or topically, thereby providing enhanced immunogenicity.

35. The method of claim 32 wherein said composition is administered to **mucosal** surfaces, thereby achieving **mucosal** immunity.

36. A method for making a nanoemulsion for administration of an immunogen, comprising the steps of: preparing a mixture comprising phospholipid and triglyceride in the weight ratio range of about 0.5:1 to 1.5:1 wherein said triglyceride has a solid to liquid phase transition temperature of greater than 25° C.; suspending said mixture in an aqueous solution at a temperature below the solid to liquid transition temperature of the triglyceride; reducing the size of the suspension to yield a nanoemulsion of lipid particles having a mean particle diameter of between about 10 nm and 250 nm; and incorporating an immunogen in the nanoemulsion.

37. The method according to claim 36 for preparing the composition of the nanoemulsion by an intrinsic procedure, where the immunogen is added before homogenization of water and oil phases.

38. The method of claim 36 for preparing the composition of the nanoemulsion by an extrinsic procedure, where the immunogen is added externally by mixing with the previously prepared plain nanoemulsion.

39. A pharmaceutical composition comprising dehydrated lipid particles

containing an antigen for administration as a nanoemulsion, wherein said lipid particles comprise a lipid core surrounded by at least one phospholipid layer, said lipid core is composed of lipid in a solid or liquid crystalline phase at least about 25° C. as determined in bulk, and said lipid particles have a mean diameter upon rehydration of about 10 to 250 nm.

40. The pharmaceutical composition of claim 39 further comprising a cryoprotectant.

41. The pharmaceutical composition of claim 40 wherein said cryoprotectant is selected from the group consisting of glucose, sucrose, lactose, maltose, trehalose, dextran, dextrin, cyclodextrin, polyvinylpyrrolidone, and amino acids.

42. The pharmaceutical composition of claim 40 wherein said cryoprotectant is present in a range of from 0.1% to 10% by weight compared to lipid.

43. The pharmaceutical composition of claim 39 wherein said lipid particles contain an immunogen.

44. A method for delivering an antigen to an animal comprising administering to said animal a pharmaceutical composition according to claim 39.

L10 ANSWER 20 OF 22 USPATFULL on STN
97:99027 Immunological tolerance-inducing agent.
Holmgren, Jan, Vastra Frolunda, Sweden
Czerkinsky, Cecil, Goteborg, Sweden
Duotol AB, Vastra Frolunda, Sweden (non-U.S. corporation)
US 5681571 19971028
APPLICATION: US 1994-184458 19940119 (8) <--
PRIORITY: SE 1993-3301 19931008
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A method of inducing immunological tolerance in a mammal to a T-cell-associated immunological response, which comprises administering by a **mucosal** route to a mammal suffering from or prone to a T-cell associated disease an immunological tolerance-inducing agent, wherein said agent comprises (i) a mucosa-binding molecule selected from the group consisting of the B subunit of cholera toxin and the B subunit of heat-labile enterotoxin of Escherichia coli, linked to (ii) a specific tolerogen associated with said T-cell associated immune response, and wherein said agent is administered in an amount and for a time effective to induce tolerance against said T-cell associated immune response.

2. A method as defined in claim 1, wherein said T-cell-associated immunological response is selected from the group consisting of: an autoimmune disorder, a tissue or cell graft rejection event, and a T-cell dependent inflammatory reaction or disorder.

3. A method as defined in claim 2, wherein said autoimmune disorder is selected from the group consisting of autoimmune diabetes, rheumatoid arthritis, multiple sclerosis, and uveoretinitis.

4. A method as defined in claim 3, wherein said autoimmune disorder is diabetes and said tolerogen is a pancreatic β-cell tolerogen.

5. A method as defined in claim 3, wherein said autoimmune disorder is multiple sclerosis and said tolerogen is a myelin-associated tolerogen.

6. A method as defined in claim 5, wherein said tolerogen is myelin basic protein.

7. A method as defined in claim 3, wherein said autoimmune disorder is uveoretinitis and said tolerogen is an eye-associated tolerogen.

8. A method as defined in claim 7, wherein said tolerogen is S-antigen.

9. A method as defined in claim 3, wherein said autoimmune disorder is rheumatoid arthritis and said tolerogen is a cartilage autoantigen.

10. A method as defined in claim 9, wherein said tolerogen is collagen.

11. A method as defined in claim 2, wherein said autoimmune disorder is selected from the group consisting of systemic lupus erythematosus

(SLE), myasthenia gravis, and autoimmune homolytic anemia (AHA).

12. A method as defined in claim 11, wherein said autoimmune disorder is SLE and said tolerogen is DNA.

13. A method as defined in claim 11, wherein said autoimmune disorder is myasthenia gravis and said tolerogen is acetylcholine receptor.

14. A method as defined in claim 2, wherein said tolerogen is a transplantation antigen.

15. A method of inducing immunological tolerance in a mammal to diabetes, which comprises administering by a **mucosal** route to a mammal suffering from or prone to diabetes an immunological tolerance-inducing agent, wherein said agent comprises (i) a mucosa-binding molecule selected from the group consisting of the B subunit of cholera toxin and the B subunit of heat-labile enterotoxin of Escherichia coli, linked to (ii) a specific tolerogen comprising insulin, and wherein said agent is administered in an amount and for a time effective to induce tolerance against said diabetes.

16. A method of inducing immunological tolerance in a mammal to rheumatoid arthritis, which comprises administering by a **mucosal** route to a mammal suffering from or prone to rheumatoid arthritis an immunological tolerance-inducing agent, wherein said agent comprises (i) a mucosa-binding molecule selected from the group consisting of the B subunit of cholera toxin and the B subunit of heat-labile enterotoxin of Escherichia coli, linked to (ii) a specific tolerogen comprising cartilage-associated collagen, and wherein said agent is administered in an amount and for a time effective to induce tolerance against said rheumatoid arthritis.

17. An immunological tolerance-inducing agent for **mucosal** administration, comprising a mucosa-binding molecule linked to a specific tolerogen, wherein (i) said mucosa-binding molecule is selected from the group consisting of the B subunit of cholera toxin and the B subunit of heat-labile enterotoxin of Escherichia coli; (ii) said mucosa-binding molecule confers binding of said agent to **mucosal** cells; (iii) said tolerogen is an autoantigen; and (iv) said agent suppresses systemic antibody production and/or delayed-type hypersensitivity to said tolerogen.

18. An agent as defined in claim 17, wherein said autoantigen is associated with systemic autoantibody production.

19. An agent as defined in claim 17, wherein said autoantigen is associated with a delayed-type hypersensitivity reaction.

20. An agent as defined in claim 17, wherein said autoantigen is associated with an autoimmune disorder, a tissue or cell graft rejection event, or a T-cell mediated inflammatory reaction or disorder.

21. An agent as defined in claim 17, wherein said mucosa-binding molecule and said tolerogen are covalently coupled to each other.

22. An agent according to claim 17, wherein said tolerogen and said mucosa-binding molecule form a hybrid molecule which is derived from expression ex vivo of a fused gene or nucleotide sequence.

23. An agent as defined in claim 17, wherein said tolerogen is insulin.

24. An agent as defined in claim 17, wherein said tolerogen is a cartilage autoantigen.

25. An agent as defined in claim 24, wherein said tolerogen is collagen.

26. An immunological tolerance-inducing agent for suppressing autoimmune diabetes, comprising a mucosa-binding molecule linked to insulin, wherein (i) said mucosa-binding molecule is the B subunit of cholera toxin or the B subunit of heat-labile enterotoxin of Escherichia coli and confers binding of said agent to **mucosal** cells and (ii) said agent suppresses autoimmune diabetes.

27. An immunological tolerance-inducing agent for suppressing multiple sclerosis, comprising a mucosa-binding molecule linked to myelin basic protein, wherein (i) said mucosa-binding molecule is the B subunit of cholera toxin or the B subunit of heat-labile enterotoxin of Escherichia coli and confers binding of said agent to **mucosal** cells; and (ii) said agent suppresses multiple sclerosis.

L10 ANSWER 21 OF 22 USPATFULL on STN
97:93891 Enterically administered recombinant poxvirus vaccines.
Small, Jr., Parker A., Gainesville, FL, United States
Bender, Bradley Stephen, Gainesville, FL, United States
Meitin, Catherine Ann, Lake Oswego, OR, United States
Moss, Bernard, Bethesda, MD, United States
University of Florida, Gainesville, FL, United States (U.S. corporation)
US 5676950 19971014
APPLICATION: US 1995-485229 19950607 (8) <--
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A method for oral or intragastric vaccine administration which comprises administering a replication deficient recombinant vaccinia or pox virus to a host under circumstances that result in delivery of said vaccine to the small intestine such that said vaccinia or pox virus is protected from exposure to stomach acid or bile, wherein said host is pre-treated, prior to said vaccine administration, such that stomach acid and bile is limited at the time that said vaccine is administered orally or intragastrically.

2. A live recombinant vaccinia pox virus or vaccinia mutant vaccine capable of expressing a heterologous polynucleotide molecule in a host, wherein said vaccine is specifically adapted to be administered to the host in a manner to induce serum IgG antibody, **mucosal IgA** antibody, and cell-mediated immune responses directed against said heterologous polynucleotide molecule expression product, wherein said specific adaptation comprises providing an enteric coating whereby the virus is released only when it reahces the host's small intestine, and wherein said vaccinia or poxvirus is replication deficient in mammals and wherein said heterologous polynucleotide molecule encodes an influenza virus hemagglutinin antigen, an influenza virus nucleoprotein antigen or both.

3. The vaccine, according to claim 2, wherein said recombinant vaccinia is MVA or said pox virus is canary pox virus.

4. The vaccine of claim 3, wherein said recombinant vaccinia or pox virus encodes bothe the influenza hemagglutinin and the nucleoprotein antigens.

5. A method for inducing a protective immune response in a host organism comprising immunizing a host with the vaccine according to claim 2, wherein said vaccine is enterically administered to the host.

6. A method for oral vaccine administration which comprises administering a replication deficient recombinant vaccinia or pox virus to a host under circumstances that result in delivery of said vaccine to the small intestine such that said vaccinia or pox virus is protected from exposure to stomach acid or bile, and wherein said replication deficient recombinant vaccinia or pox virus encodes an influenza virus hemagglutinim antigen, an influenza virus nucleoprotein antigen, or both.

7. The method of claim 6, wherein said recombinant vaccinia or pox virus encodes both the influenza hemagglutinin and the nucleoprotein antigens.

8. The method of claim 1 for oral vaccine administration which comprises: a) preparing a replication deficient recombinant vaccinia or pox virus; b) pre-treating a host in need of vaccination with an acid-release blocker or a cholecystokinin antagonist or both prior to orally administering said recombinant virus; and c) orally administering said recombinant virus.

9. The method of claim 8 wherein said virus is a recombinant MVA.

10. The method of claim 9 wherein said recombinant MVA comprises at least one influenza virus gene.

11. The method of claim 10 wherein said recombinant MVA contains an influenza virus hemagglutinin gene, an influenza virus nucleoprotein gene or both.

12. The method of claim 11 wherein said recombinant MVA is enterically coated.

L10 ANSWER 22 OF 22 USPATFULL on STN
96:43382 Vaccine compositions and method for induction of **mucosal** immune response via systemic vaccination.
Daynes, Raymond A., Park City, UT, United States
Araneo, Barbara A., Salt Lake City, UT, United States
University of Utah Research Foundation, Salt Lake City, UT, United States (U.S. corporation)
US 5518725 19960521
APPLICATION: US 1993-123844 19930909 (8) <--
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A method for inducing an antigen-specific **mucosal** immune response in a vertebrate animal, which comprises administering an effective amount of at least one lymphoid organ modifying agent to the vertebrate animal at a peripheral, non-**mucosal** site which drains into a peripheral lymphoid organ or compartment, and administering an effective amount of a specific antigen to the vertebrate animal at a peripheral, non-**mucosal** site which drains into said peripheral lymphoid organ or compartment, said lymphoid organ modifying agent selected from the group consisting of all trans-retinoic acid and $1,25(OH)_2$ D_3.

2. The method of claim 1 wherein said lymphoid organ modifying agent comprises $1,25(OH)_2$ D_3.

3. The method of claim 1 wherein said lymphoid organ modifying agent comprises all trans-retinoic acid.

4. The method of claim 1 wherein said lymphoid organ modifying agent is administered epicutaneously.

5. The method of claim 1 wherein said lymphoid organ modifying agent is administered intramuscularly.

6. The method of claim 1 wherein said lymphoid organ modifying agent is administered intradermally.

7. The method of claim 1 wherein said lymphoid organ modifying agent is administered subcutaneously.

8. The method of claim 1 wherein said effective amount of said lymphoid organ modifying agent is 0.01-5.0 μg/kg body weight.

9. The method of claim 1 wherein said effective amount of said lymphoid organ modifying agent is in the range of 0.1-500 μg.

10. The method of claim 1 wherein said lymphoid organ modifying agent administering step commences at a time up to three hours earlier than the time said specific antigen administering step commences.

11. The method of claim 1 wherein said lymphoid organ modifying agent administering step commences at about the same time as said specific antigen administering step commences.

12. The method of claim 1 wherein said lymphoid organ modifying agent administering step commences at a time up to five days later than the time said specific antigen administering step commences.

13. The method of claim 10 wherein said lymphoid organ modifying agent administering step and said specific antigen administering step are carried out at least partly concurrently.

14. The method of claim 11 wherein said lymphoid organ modifying agent administering step and said specific antigen administering step are carried out at least partly concurrently.

15. The method of claim 12 wherein said lymphoid organ modifying agent administering step and said specific antigen administering step are carried out at least partly concurrently.

16. The method of claim 1 wherein said specific antigen and said lymphold organ modifying agent are combined prior to said administering steps.

17. The method of claim 1 which further comprises administering an effective amount of an immune response augmenting agent, said immune response augmenting agent having the formula ##STR4## wherein R^1 is .dbd.O; R^2 is H or halogen; R^3 is H with a 5-6 double bond;

R^4 is OR^5 ; R^5 is H, SO_2 OM, or PO_2 OM; M is H, Na, K or ##STR5## and R^6 and R^7 may be the same or different and may be a straight or branched C_{1-4} alkyl.

18. The method of claim 17, wherein R^1 is .dbd.O , R^2 is H, R^3 is H with a 5-6 double bond, and R^4 is OH.

19. The method of claim 17, wherein R^1 is .dbd.O , R^2 is Br, R^3 is H with a 5-6 double bond, and R^4 is OH.

20. The method of claim 17, wherein R^1 is .dbd.O , R^2 is H, R^3 is H with a 5-6 double bond, and R^4 is OSO_2 M.

21. The method of claim 17, wherein R^1 is .dbd.O , R^2 is H, R^3 is H with a 5-6 double bond, and R^4 is OPO_2 M.

22. The method of claim 17 wherein said lymphoid organ modifying agent comprises 1,25$(OH)_2$ D_3.

23. The method of claim 17 wherein said lymphoid organ modifying agent comprises all trans-retinoic acid.

24. The method of claim 18 wherein said lymphoid organ modifying agent comprises 1,25$(OH)_2$ D_3.

25. The method of claim 18 wherein said lymphoid organ modifying agent comprises all trans-retinoic acid.

26. The method of claim 17 wherein said effective amount of immune response augmenting agent is 10-1,000 μg when administration is by injection, or 10-100 mg/day when administration is oral.

27. The method of claim 17 wherein said immune response augmenting agent is administered separately from said lymphoid organ modifying agent.

28. The method of claim 27 wherein said immune response augmenting agent is administered up to three hours prior to said lymphoid organ modifying agent.

29. The method of claim 17 wherein said immune response augmenting agent is administered concurrently with said lymphoid organ modifying agent.

30. The method of claim 17 wherein said immune response augmenting agent is administered separately from said lymphold organ modifying agent and said antigen.

31. The method of claim 30 wherein said immune response augmenting agent is administered up to three hours prior to said lymphoid organ modifying agent and said antigen.

32. The method of claim 30 wherein said immune response augmenting agent is administered up to three hours after said lymphoid organ modifying agent and said antigen.

33. The method of claim 17 wherein said antigen, lymphoid organ modifying agent and said immune response augmenting agent are combined prior to administration.

34. A method for inducing production of antigen-specific antibodies in the mammary secretions of a female mammal, comprising treating the female mammal according to the method of claim 1.

35. A method for inducing production of antigen-specific antibodies in the mammary secretions of a female mammal, comprising treating the female mammal according to the method of claim 17.

36. A method for conferring a specific passive immunity to a suckling mammal, comprising permitting the suckling mammal to consume mammary secretions from a female mammal treated according to the method of claim 1.

37. A method for conferring a specific passive immunity to a suckling mammal, comprising permitting the suckling mammal to consume mammary secretions from a female mammal treated according to the method of claim 17.

38. A vaccine composition comprising an effective amount of at least one lymphoid organ modifying agent and an effective amount of a specific

antigen in a pharmaceutically acceptable carrier to induce an antigen-specific **mucosal** immune response, said lymphoid organ modifying agent is selected from the group consisting of all trans-retinoic acid and $1,25(OH)_2$ D_3.

39. The vaccine composition of claim 38 wherein said lymphoid organ modifying agent comprises $1,25(OH)_2$ D_3.

40. The vaccine composition of claim 38 wherein said lymphoid organ modifying agent comprises all trans-retinoic acid.

41. The vaccine composition of claim 38 which further comprises an effective amount of an immune response augmenting agent, said immune response augmenting agent having the formula ##STR6## wherein R^1 is .dbd.O; R^2 is H or halogen; R^3 is H with a 5-6 double bond; R^4 is OR^5 ; R^5 is H, SO_2 OM, or PO_2 OM M is H, Na, K or ##STR7## and R^6 and R^7 may be the same or different and may be a straight or branched C_{1-14} alkyl.

42. The vaccine composition of claim 41, wherein R^1 is .dbd.O, R^2 is H, R^3 is H with a 5-6 double bond and R^4 is OH.

43. The vaccine composition of claim 41, wherein R^1 is .dbd.O, R^2 is Br, R^3 is H with a 5-6 double bond, and R^4 is OH.

44. The vaccine composition of claim 41, wherein R^1 is .dbd.O, R^2 is H, R^3 is H with a 5-6 double bond, and R^4 is OSO_2 M.

45. The vaccine composition of claim 41, wherein R^1 is .dbd.O, R^2 is H, R^3 is H with a 5-6 double bond, and R^4 is OPO_2 M.

46. The vaccine composition of claim 41 wherein said lymphoid organ modifying agent comprises $1,25(OH)_2$ D_3.

47. The vaccine composition of claim 41 wherein said lymphoid organ modifying agent comprises all trans-retinoic acid.

48. The vaccine composition of claim 42 wherein said lymphoid organ modifying agent comprises $1,25(OH)_2$ D_3.

49. The vaccine composition of claim 42 wherein said lymphoid organ modifying agent comprises all trans-retinoic acid.

50. The vaccine composition of claim 38 wherein said antigen is capable of eliciting an immune response against viral hepatitis, influenza, diphtheria, tetanus, pertussis, measles, mumps, rubella, polio, pneumococcus, herpes, respiratory syncytial virus, haemophilus influenza type b, varicella-zoster virus or rabies.

51. The vaccine composition of claim 39 wherein said antigen is capable of eliciting an immune response against viral hepatitis, influenza, diphtheria, tetanus, pertussis, measles, mumps, rubella, polio, pneumococcus, herpes, respiratory syncytial virus, haemophilus influenza type b, varicella-zoster virus or rabies.

52. The vaccine composition of claim 40 wherein said antigen is capable of eliciting an immune response against viral hepatitis, influenza, diphtheria, tetanus, pertussis, measles, mumps, rubella, polio, pneumococcus, herpes, respiratory syncytial virus, haemophilus influenza type b, varicella-zoster virus or rabies.

53. The vaccine composition of claim 41 wherein said antigen is capable of eliciting an immune response against viral hepatitis, influenza, diphtheria, tetanus, pertussis, measles, mumps, rubella, polio, pneumococcus, herpes, respiratory syncytial virus, haemophilus influenza type b, varicella-zoster virus or rabies.

54. The vaccine composition of claim 42 wherein said antigen is capable of eliciting an immune response against viral hepatitis, influenza, diphtheria, tetanus, pertussis, measles, mumps, rubella, polio, pneumococcus, herpes, respiratory syncytial virus, haemophilus influenza type b, varicella-zoster virus or rabies.

55. The vaccine composition of claim 44 wherein said antigen is capable of eliciting an immune response against viral hepatitis, influenza, diphtheria, tetanus, pertussis, measles, mumps, rubella, polio,

pneumococcus, herpes, respiratory syncytial virus, haemophilus influenza type b, varicella-zoster virus or rabies.

56. The method of claim 20 wherein said lymphoid organ modifying agent comprises $1,25(OH)_2$ D_3.

57. The method of claim 20 wherein said lymphoid organ modifying agent comprises all trans-retinoic acid.

58. The vaccine composition of claim 44 wherein said lymphoid organ modifying agent comprises $1,25(OH)_2$ D_3.

59. The vaccine composition of claim 44 wherein said lymphoid organ modifying agent comprises all trans-retinoic acid.

60. The vaccine composition of claim 38 which comprises 0.1-500 μg of lymphoid organ modifying agent.

61. The vaccine composition of claim 41 which comprises 0.1-500 μg of lymphoid organ modifying agent.

62. The vaccine composition of claim 41 which comprises 10-1,000 μg of immune response augmenting agent.

63. The vaccine composition of claim 62 which comprises 0.1-500 μg of lymphoid organ modifying agent.

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     (FILE 'HOME' ENTERED AT 11:40:40 ON 22 AUG 2005)

     FILE 'MEDLINE' ENTERED AT 11:41:54 ON 22 AUG 2005
L1        155517 S (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L2          1953 S L1 AND (MUCOSAL OR IGA)
L3           420 S L2 AND (ENV? OR GP160 OR GP120 OR GP41)
L4            99 S L3 AND PY<1997
L5            22 S L4 AND NEUTRALIZ?

     FILE 'USPATFULL' ENTERED AT 11:59:54 ON 22 AUG 2005
L6         40702 S (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L7         10049 S L6 AND (MUCOSAL OR IGA)
L8          1708 S L7 AND (GP160 OR GP120 OR GP41)
L9           131 S L8 AND (MUCOSAL/CLM)
L10           22 S L9 AND AY<1997

=> log off
ALL L# QUERIES AND ANSWER SETS ARE DELETED AT LOGOFF
LOGOFF? (Y)/N/HOLD:y
STN INTERNATIONAL LOGOFF AT 12:05:00 ON 22 AUG 2005
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